# Dealing with Heterogeneity in Cost-Effectiveness Analysis

## Appraisal Committee View

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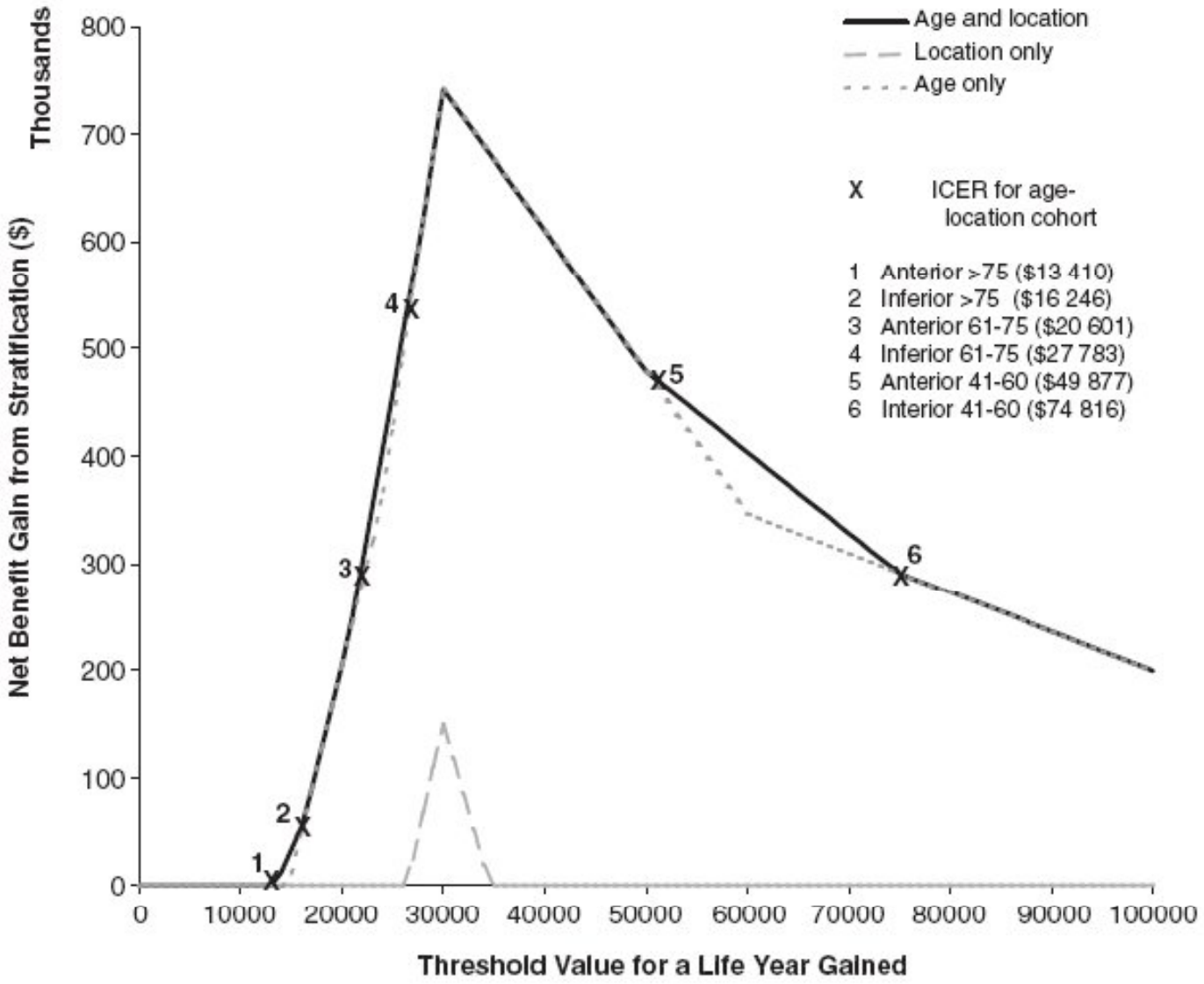
# Outline

- Key concepts and starting points
- Heterogeneity in baseline risks
- Heterogeneity in treatment effect
- Other types of heterogeneity

# Decision making context

- Objective to maximise value from limited health care budgets
- Health gains from new technologies are greater than health gains displaced
- Costs and effects differ between patients
- Restricted use: give to the sub-groups in which therapy most cost-effective
- Decision making needs analysis appropriate for its needs
- Results in some differences from conventional trials perspective

# The gains from ‘stratification’




Source: Coyle *et al.* *Health Economics*, 2002

# What is net benefit?

$$NB_i = (QALY_i \times \lambda) - Cost_i$$

$\lambda$ = The 'value' of a QALY; e.g. the cost-effectiveness threshold

Alternatively: $NB_i / \lambda$ = net health effect (in QALYs)

# Sources of heterogeneity in patients

- Baseline risks
- Relative treatment effects (e.g. hazard ratios)
- Prognosis given an event
- Costs
- Preferences
- Location of treatment

# Heterogeneity in baseline event rates

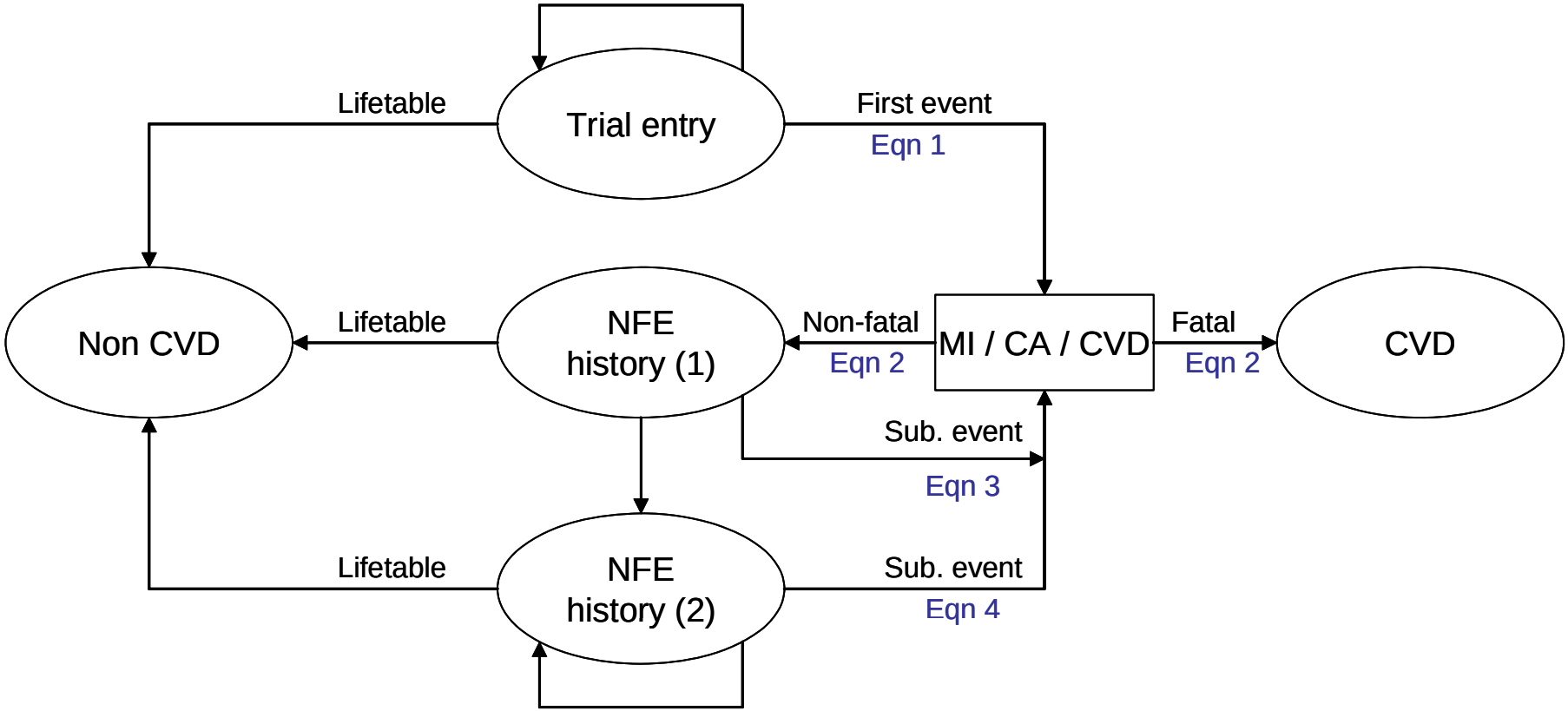
## Example of EUROPA analysis

- Cost-effectiveness of Perindopril versus usual care in stable angina
- Individual patient data on 12,218 patients from EUROPA trial
- Benefits driven by reduction in the risk of cardiac events
- Heterogeneity in baseline risk but not treatment effect

Briggs, Mihaylova, Sculpher *et al.* Cost-effectiveness of perindopril in reducing cardiovascular events in patients with stable coronary artery disease using data from the EUROPA Study. *Heart,* in press.

# EUROPA example

## Model structure



# EUROPA example

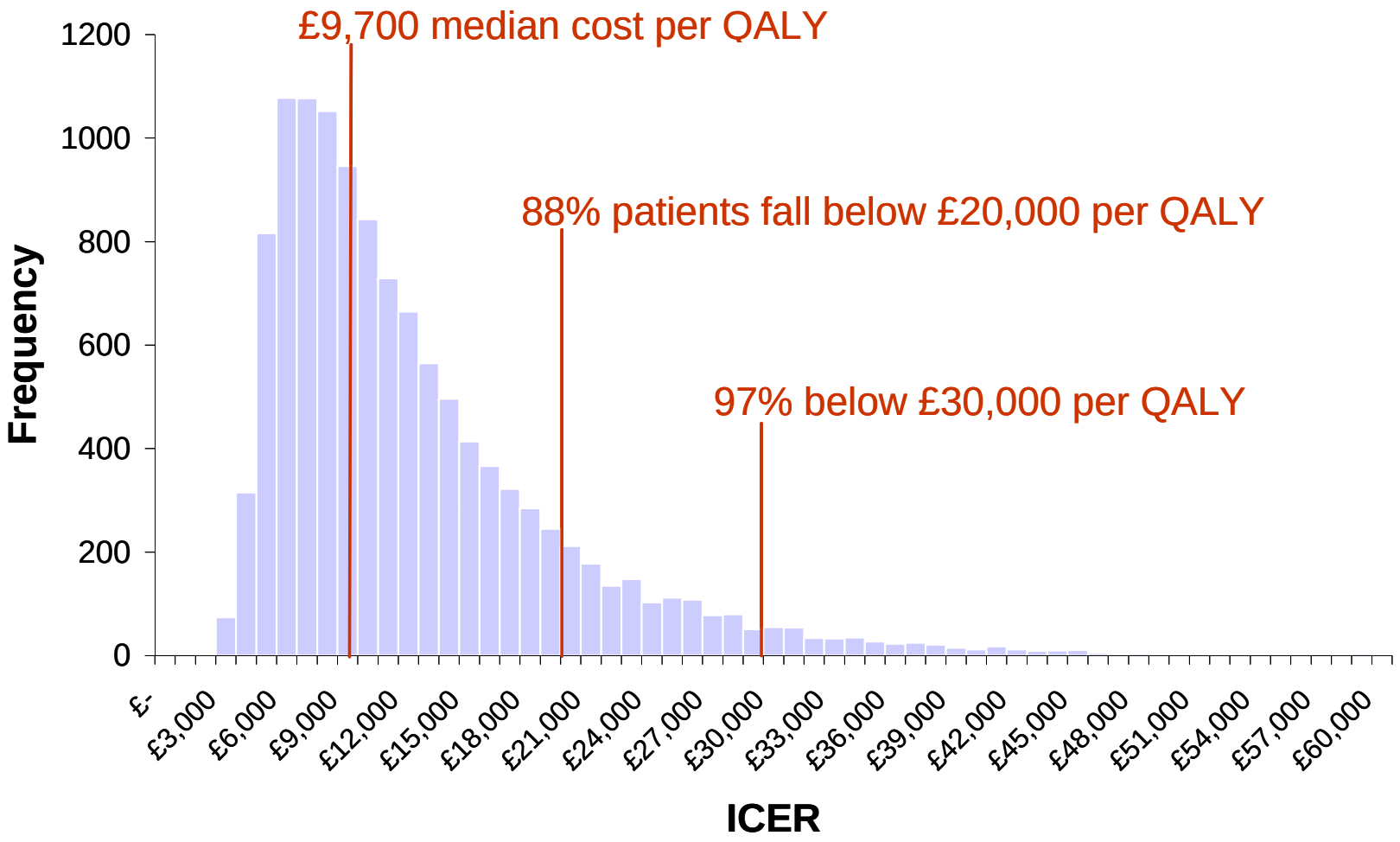
## Equation 1(1,069 events)

| Explanatory baseline characteristics | Hazard Ratio | Lower 95% limit | Upper 95% limit |
|---|---|---|---|
| Use of Perindopril | 0.81 | 0.71 | 0.91 |
| Age (years greater than age 65) | 1.06 | 1.04 | 1.08 |
| Male | 1.54 | 1.28 | 1.87 |
| Smoker | 1.49 | 1.27 | 1.74 |
| Previous MI | 1.44 | 1.26 | 1.66 |
| Previous revascularisation | 0.88 | 0.77 | 0.99 |
| Existing vascular disease[b] | 1.69 | 1.44 | 1.98 |
| Diabetes Mellitus | 1.49 | 1.28 | 1.74 |
| Family history of coronary artery disease | 1.21 | 1.05 | 1.38 |
| Symptomatic angina[c] or history of heart failure | 1.32 | 1.16 | 1.51 |
| Systolic blood pressure | 1.00 | 1.00 | 1.01 |
| Units creatinine clearance below 80ml/min | 1.01 | 1.00 | 1.02 |
| BMI > 30 (obese) | 1.41 | 1.22 | 1.63 |
| Total cholesterol | 1.13 | 1.07 | 1.20 |
| Using nitrates at baseline | 1.42 | 1.25 | 1.63 |
| Using calcium channel blockers at baseline | 1.20 | 1.06 | 1.36 |
| Using lipid lowering therapy at baseline | 0.86 | 0.75 | 0.97 |
| Constant term (on the log scale) | -12.27 | -12.97 | -11.57 |

Composite endpoint: Primary trial endpoint of cardiovascular mortality, myocardial infarction or cardiac arrest.

# EUROPA example

## Predicted cost-effectiveness of perindopril



# When are such methods appropriate?

- Clear heterogeneity in baseline risks
  - Relevant to some diseases more than others
  - How do we select covariates?
- Need access to individual patient data
  - Control group from RCT
  - Longitudinal observational studies
- Acceptability of assumption of no interaction with treatment effect
- Not just when ‘average’ cost-effectiveness is hard to show

# Heterogeneity in relative treatment effects

## RITA-3 example

| | First quartile* | Second quartile* | Third quartile* | Fourth lower quartile* | Fourth upper quartile* |
|---|---|---|---|---|---|
| Age | 45 | 52 | 52 | 61 | 66 |
| Diabetes | 0 | 0 | 0 | 0 | 1 |
| Previous myocardial infarction | 0 | 0 | 1 | 1 | 1 |
| Smoker | 0 | 1 | 0 | 1 | 0 |
| Pulse | 8 | 10 | 10 | 11 | 13 |
| ST depression | 0 | 0 | 1 | 1 | 1 |
| Angina | 1 | 0 | 1 | 0 | 0 |
| Male | 0 | 1 | 1 | 1 | 1 |
| Left bundle branch block | 0 | 0 | 0 | 0 | 0 |
| | | | | | |
| ICER (no interaction) | 49,754 | 22,145 | 20,765 | 11,682 | 12,490 |
| ICER (interaction) | 783,283 | 42,877 | 27,626 | 11,702 | 10,190 |

Henriksson *et al.* The cost-effectiveness of an early interventional strategy in non-ST-elevation acute coronary syndrome based on the RITA 3 trial. Presented at Society of Medical Decision Making, October 2006

# Heterogeneity in costs

## EUROPA example - cost equation

| Covariate | Cost | SE |
|---|---|---|
| NFE | 9,775 | 428 |
| NFEhistory | 816 | 117 |
| Fatal event | 3,015 | 367 |
| NCD | 10,285 | 889 |
| Age in years | 11 | 2 |
| Existing vascular disease | 325 | 62 |
| Diabetes mellitus | 209 | 56 |
| Symptomatic angina or heart failure | 234 | 41 |
| Creatinine clearance below 80ml/min | 7 | 2 |
| Using nitrates at baseline | 226 | 33 |
| Using calcium channel blockers at baseline | 157 | 34 |
| Using lipid lowering therapy at baseline | 100 | 32 |
| Treated in UK | -88 | 39 |
| (constant) | -17 | 121 |

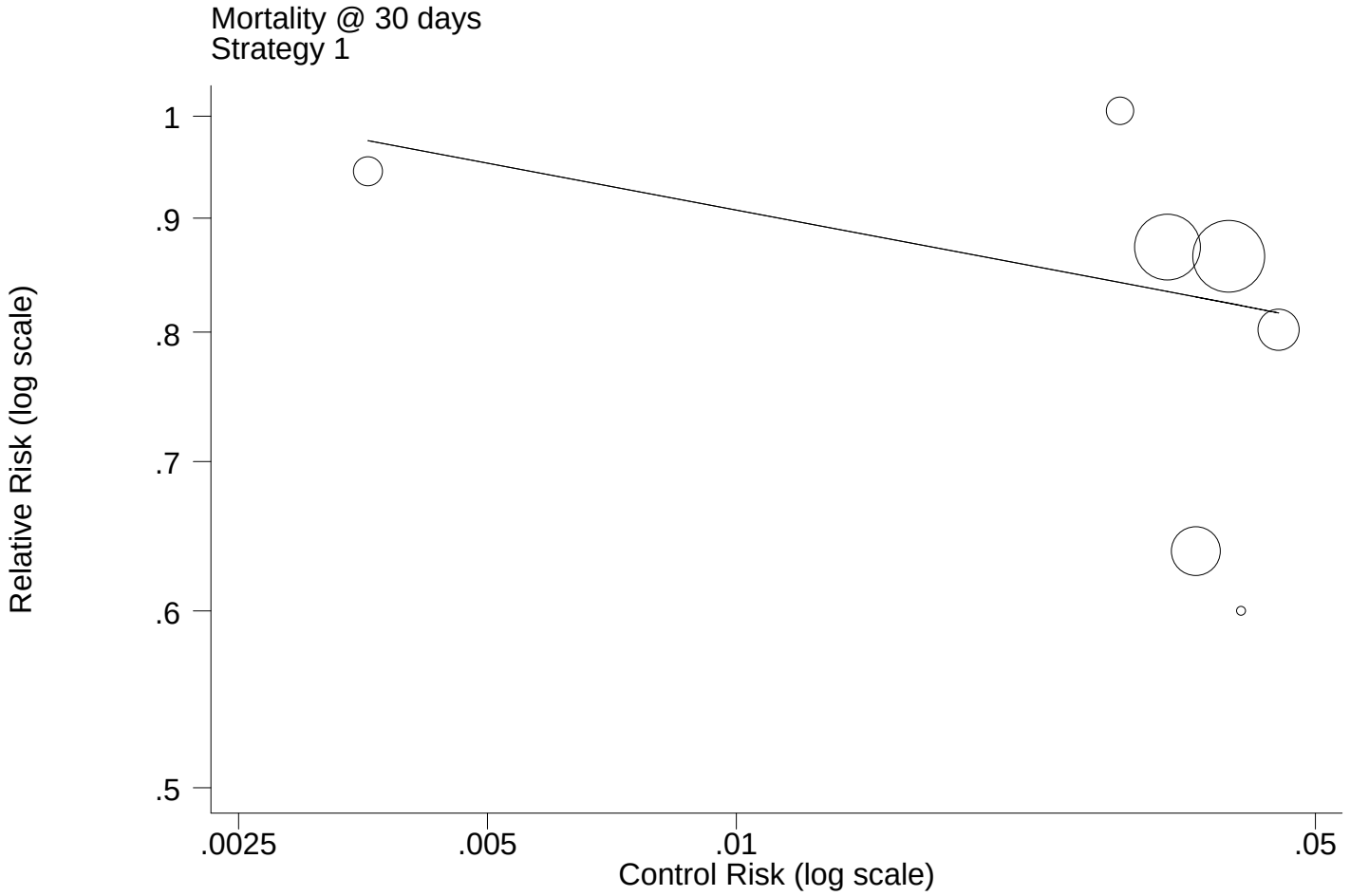
Note: Costs include days in hospital and non-study drugs

# What do we do when we have no individual patient data?

- Examples come from single source of individual patient data
- Often with a model will take baseline risks and relative treatment effect(s) from different sources
- Assumption of independence common
- In meta-analysis may be able to assess assumption and adjust accordingly

# Example – glycoprotein IIb/IIIa antagonists in ACS

## The relationship between baseline risk and relative risk




Sculpher MJ, *et al.* Generalisability in economic evaluation studies in health care: a review and case studies. *Health Technology Assessment* 2004;8(49).

# Different views on heterogeneity in treatment effect

| EBM | Decision analysts |
|---|---|
| Clinically plausible | Clinically plausible |
| Pre-defined | Pre-defined |
| Statistically significant | Implementable (at a cost) |
| Accompanied by a statistically significant overall effect | Uncertainty expressed |
| Few of them | |

Rules on the use of sub-groups impose costs

# Other types of heterogeneity

- Prognosis
- In preferences
- Between locations
- Variability in responses (post baseline)

# What about equity/ethical issues?

- Socio-demographic variables (e.g. age, sex, race) can affect cost-effectiveness in a number of ways
  - Relative treatment effects
  - Baseline event risks
  - Prognosis
- In terms of equity, (some of) these may not be appropriate
- But equity rules impose costs
- For decision making:
  - Have clear rules of what is considered appropriate
  - Present costs of operating ‘equity rules’

# Issues of NICE process

- Clear statement principles
  - Importance of sub-groups
  - Costs of ignoring
  - Appropriate means of identification and analysis
- What is the role of pre-specification
  - What types of sub-groups?
  - How much can be agreed in the scope?
- Quantification of uncertainty
  - Decision rather than parameter uncertainty
  - How is it to be used by the Appraisal Committee

# Summary

- Heterogeneity prevails in most clinical context
- Different types of heterogeneity
- Mismatch between trials orthodoxy for sub-groups and needs of decision making
- But this does mean ‘anything goes’
  - Plausibility is essential
  - There is a role for pre-specification
  - (Decision) uncertainty needs to be reflected