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## Exploring uncertainty in cost effectiveness analysis

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# Why uncertainty is important for decisions?

- All decisions are associated with a risk that a more optimal course of action could have been achieved
- All economic evaluations contain uncertainty
- Characterising uncertainty will enable decision makers to have the option of an informed choice to reduce uncertainty, e.g. delaying implementation



# Reasons for uncertainty over cost effectiveness results

- Uncertainty over treatment effects
  - confidence intervals around estimates from trials/meta-analysis
  - uncertainty due to queries over internal/external validity of trials?
- Uncertainty over other data inputs
  - baseline risks, costs, utilities,...
  - may be quantitative estimates of sampling error (CIs)
  - but may also need to estimate ranges more informally
- Assumptions and model structure
  - cannot be represented as confidence interval
  - may test impact of changing assumptions in sensitivity analysis



# Uncertainty versus variability

- **Variability** (“first-order” uncertainty)
  - Natural variation among individuals in their response to treatment and the costs they incur
  - Reflected in standard deviations in a mean value
  - Further evidence will not reduce this variation
  - **NOTE** heterogeneity – differences between patients that can (in part) *be explained*, e.g. age, sex
- **Uncertainty**
  - Cannot know for certain what the expected (mean) costs and effects of a particular treatment will be when provided for a given population
  - Further evidence can reduce this uncertainty providing more precise estimates of these mean costs and health effects (e.g. bigger studies with reduce CI and SE for estimated parameters)



# Type of uncertainty

- **Methodological uncertainty**
  - Methodological disagreement among analysts e.g. rate of discounting, method for costing
- **Modelling uncertainty**
  - The uncertainty due to the model 'structure' relating to the function form of the model
- **Parameter uncertainty**
  - The uncertainty in parameter inputs to a study that includes sampling variation
- **Generalizability/Transferability**
  - Using economic evaluation results conducted in one setting in other settings



# “Methodological uncertainty” – the role of the ‘Reference Case’

- Debate about the most appropriate methods to use for some aspects of health technology assessment.
- Can relate to choices that are essentially value judgements; for example, whose preferences to use for valuation of health outcomes.
- It also includes methodological choices that relate to more technical aspects of an analysis; for example, the most appropriate approach to measuring health-related quality of life (HRQL).
- A reference case specifies the methods considered by the decision making body to be the most appropriate for its purpose
- An RF facilitates a consistent approach, but does not necessarily exclude non-RF analyses, especially if strict adherence to the RF is not possible.
- Issues – implementing changes over time; disagreement



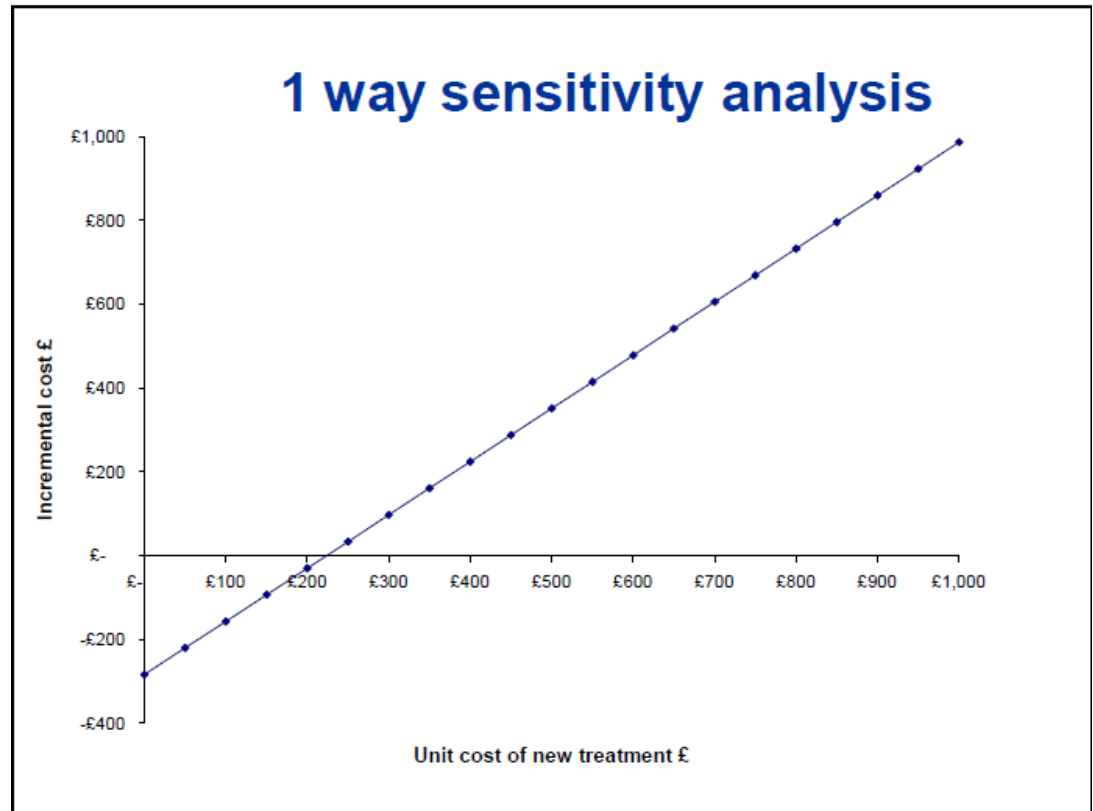
# Handling parameter uncertainty

- Sensitivity analysis: model results that reflect different possible values for model inputs
- Type of sensitivity analysis
  - Deterministic: One-way, multi-way, extreme, threshold
  - Probabilistic



# One-way sensitivity analysis

- One parameter in the estimation model is set to vary across a reasonable range one at a time.
- The resulted cost, effectiveness, and ICER are determined how sensitive they are with respect to the varying range.





# Extreme

The cost and effectiveness of the intervention of interest are evaluated given the model parameters that are based on the best case vs the worst case scenarios and yield the extreme value of ICER.

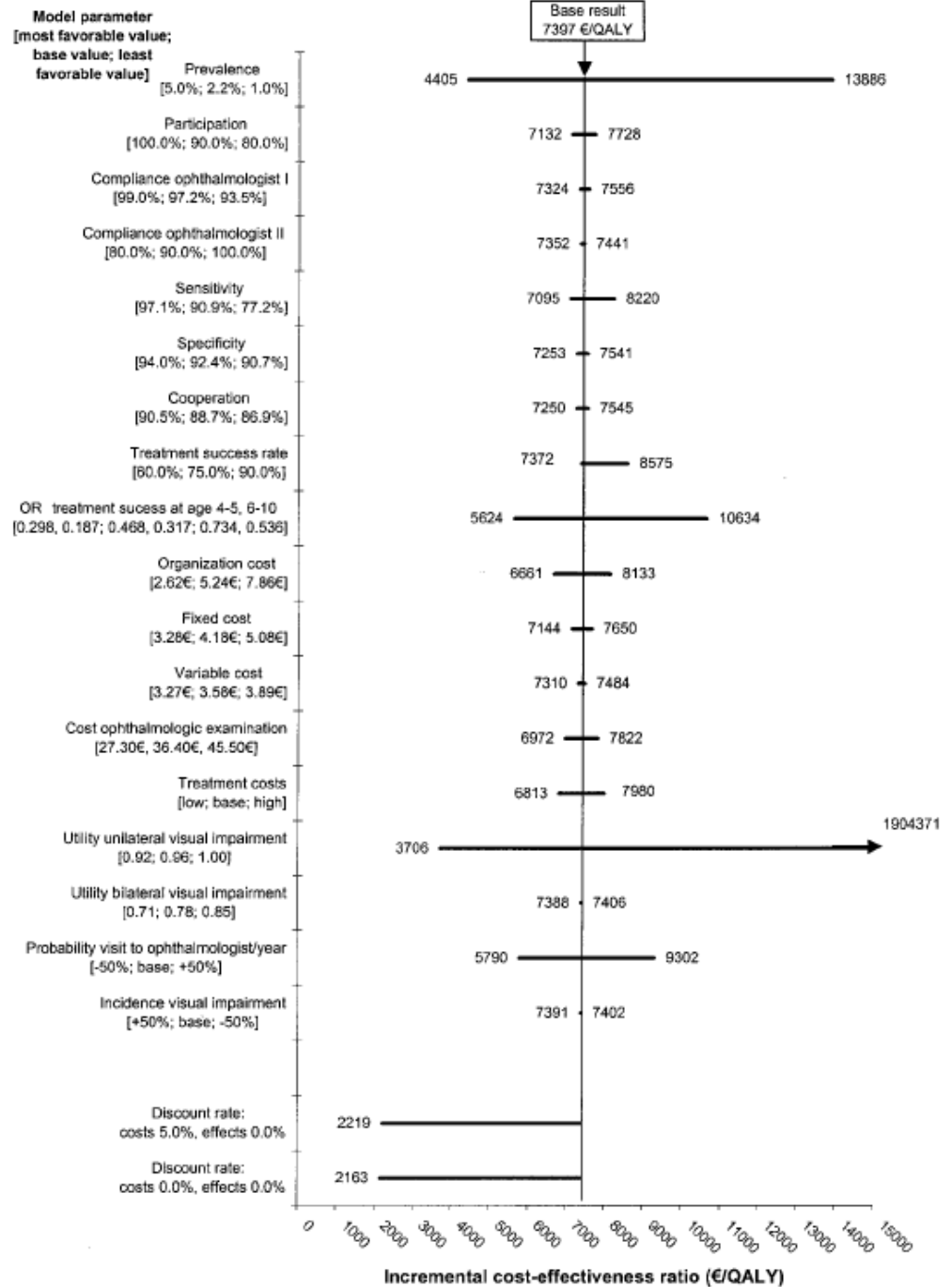


Fig 3. Results of univariate sensitivity analysis.



# Threshold

Table 5. Results of One-Way Sensitivity Analyses\*

Variable	Base-Case Estimate	Threshold	Comment
Cost per coxib tablet, \$	2.66	0.25	If less than threshold, then coxib strategy becomes dominant
Coxib pills consumed daily, <i>n</i>	1.0	0.2	If less than threshold, then coxib strategy becomes dominant
Probability of upper-gastrointestinal dyspeptic symptoms in patients receiving naproxen, %	10.9	42	If greater than threshold, then coxib strategy becomes dominant
Rate of clinically significant ulcer complications with naproxen over lifetime horizon, %	7.2	40	If greater than threshold, then coxib strategy becomes dominant
Cost per naproxen tablet, \$	0.18	2.17	If greater than threshold, then coxib strategy becomes dominant

\* The listed thresholds are the values at which the coxib strategy becomes dominant (that is, becomes more effective and less expensive than the naproxen strategy).

Spiegel et al. *Ann Intern Med.* 2003; 138: 795-806.

The critical value(s) of a parameter or parameters central to the decision are identified.

# Problem with deterministic result presentation

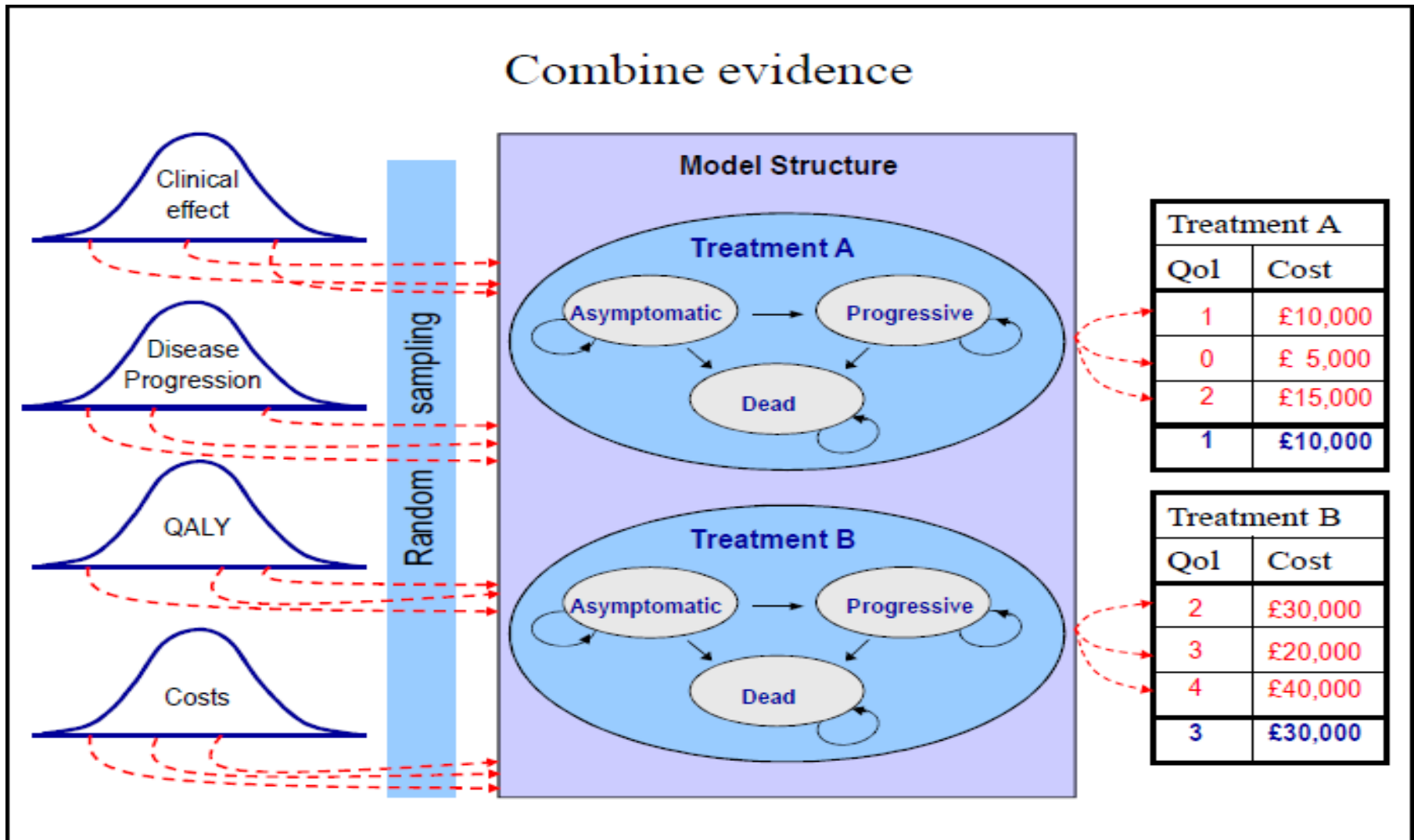
- Ranges
- Interaction
- Difficult / complex
- Interpretation
- Summary statement

# Probability sensitivity analysis

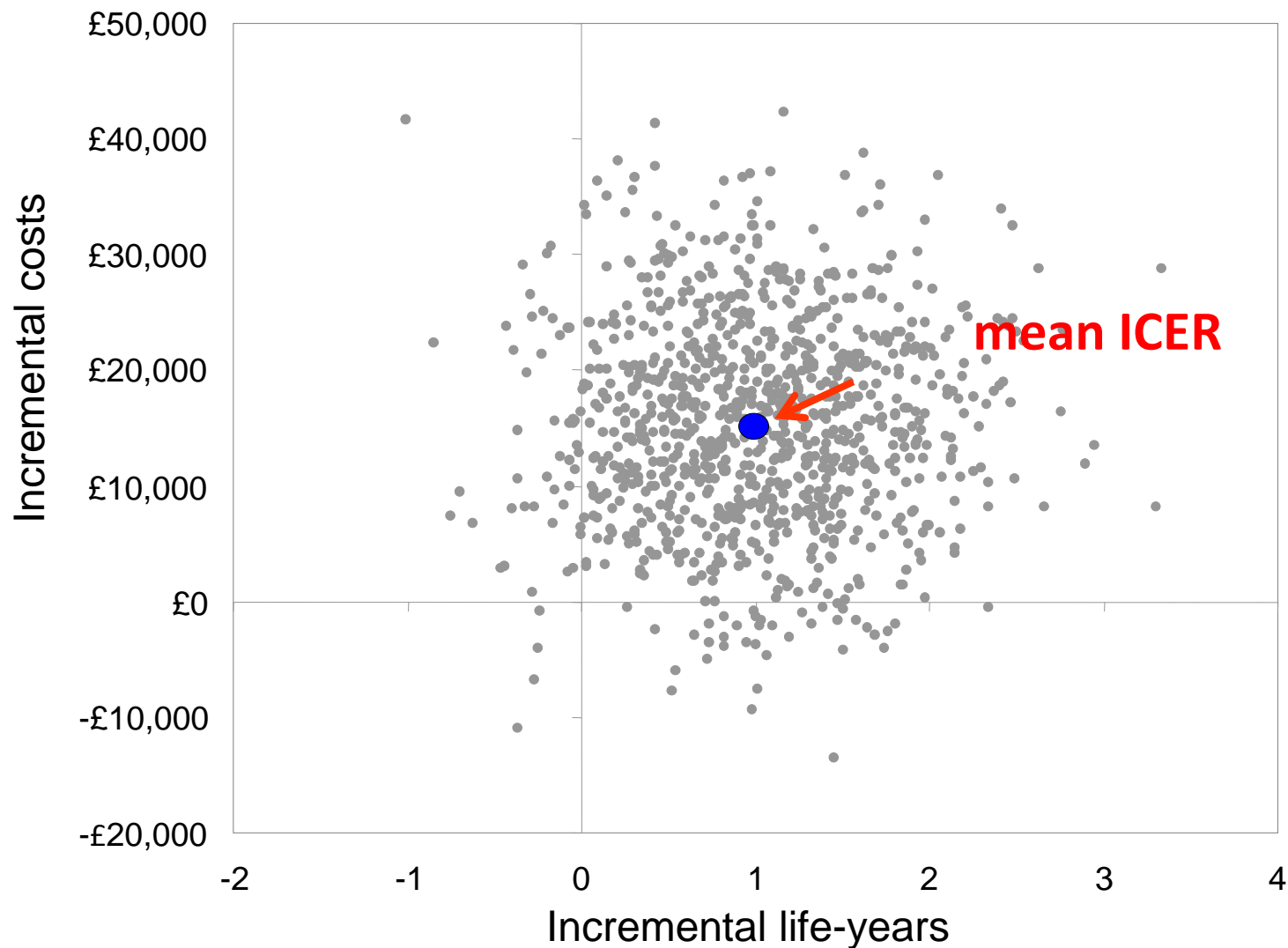
- Take all parameter uncertainty into account
- Require a knowledge on mathematical modelling in programmes such as Microsoft Excel®



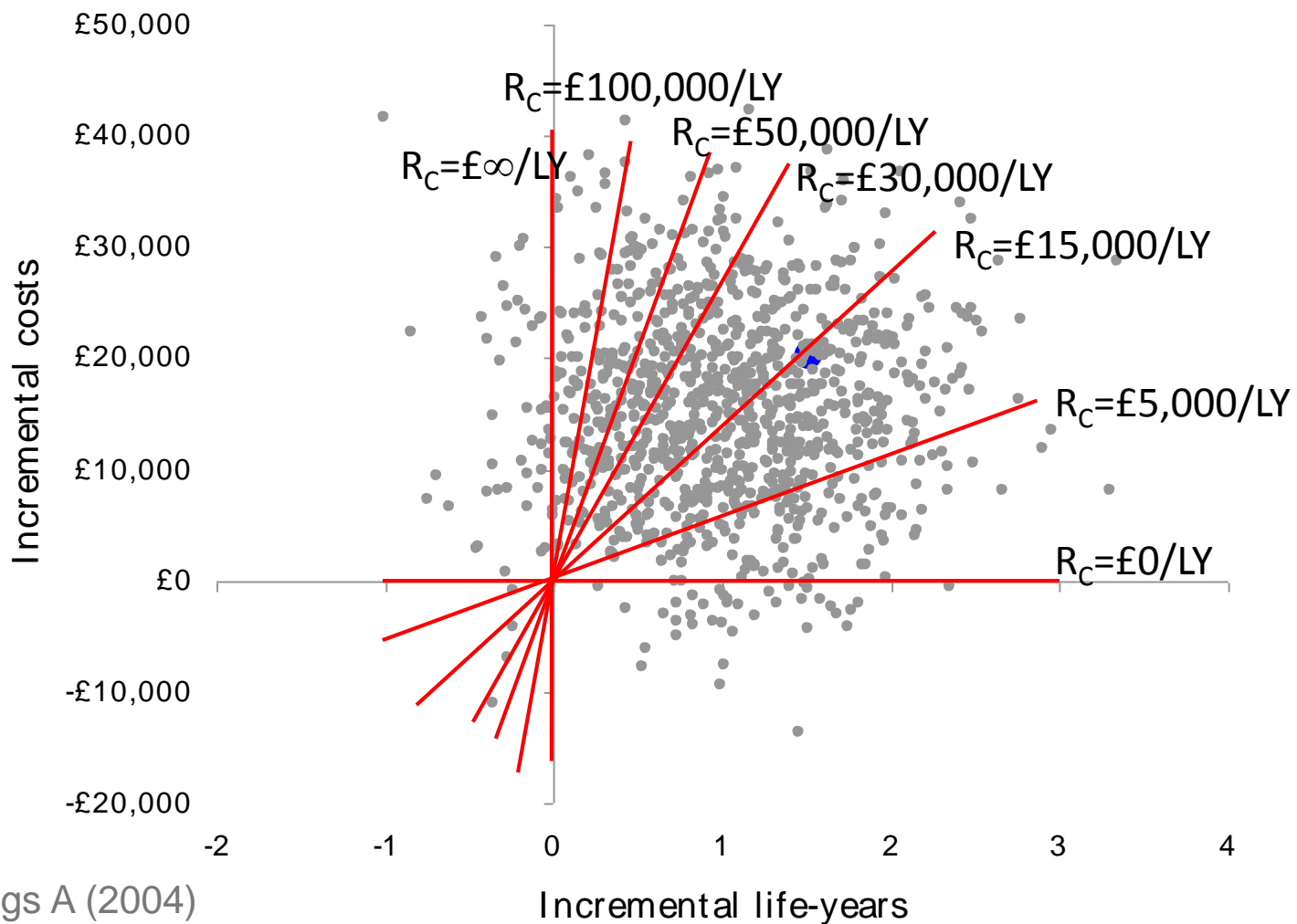
# Probability Sensitivity Analysis (PSA)



# Simulation results from probabilistic model

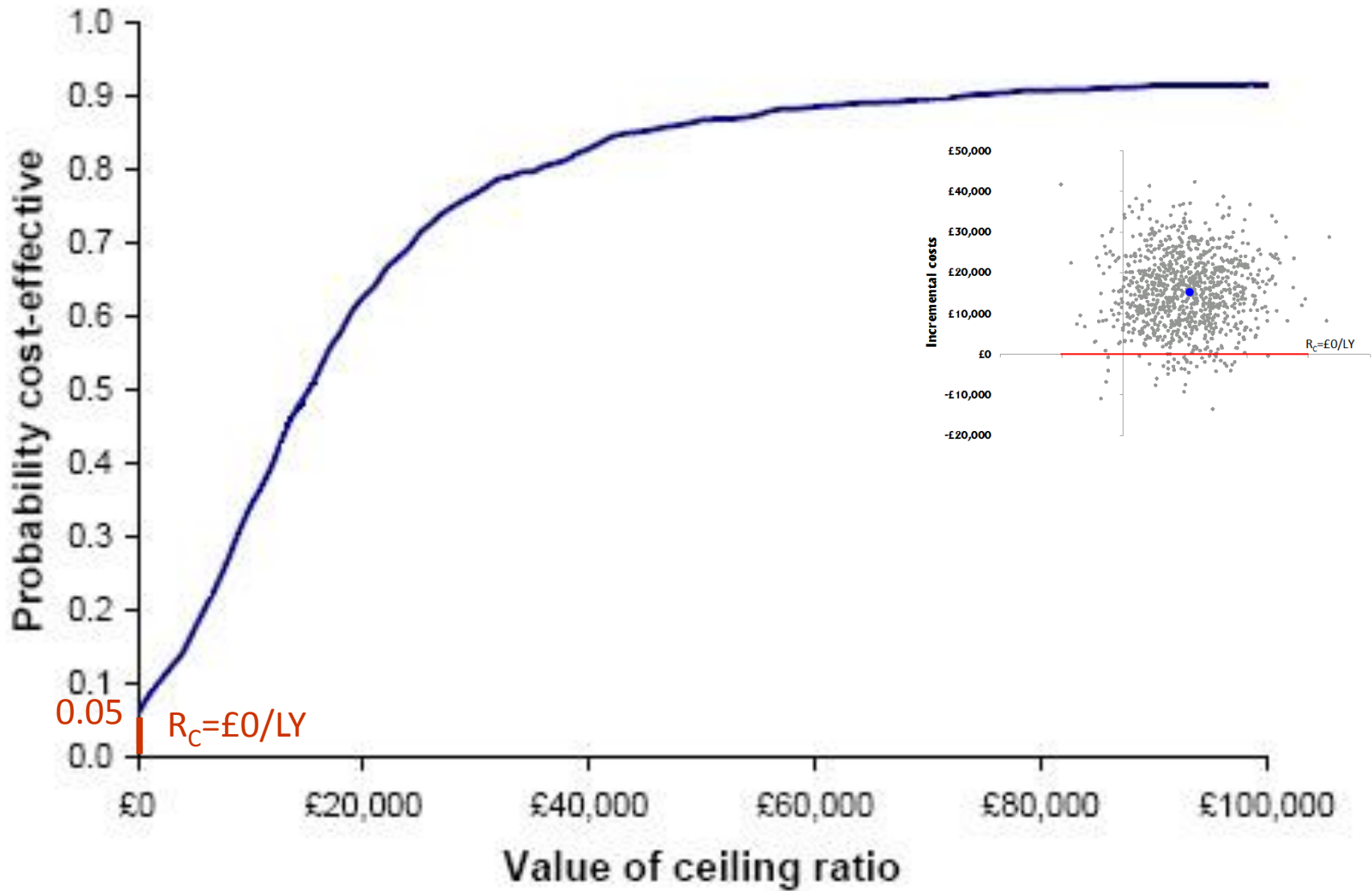


# Uncertainty on the CE plane: using the decision rule



Source: Briggs A (2004)

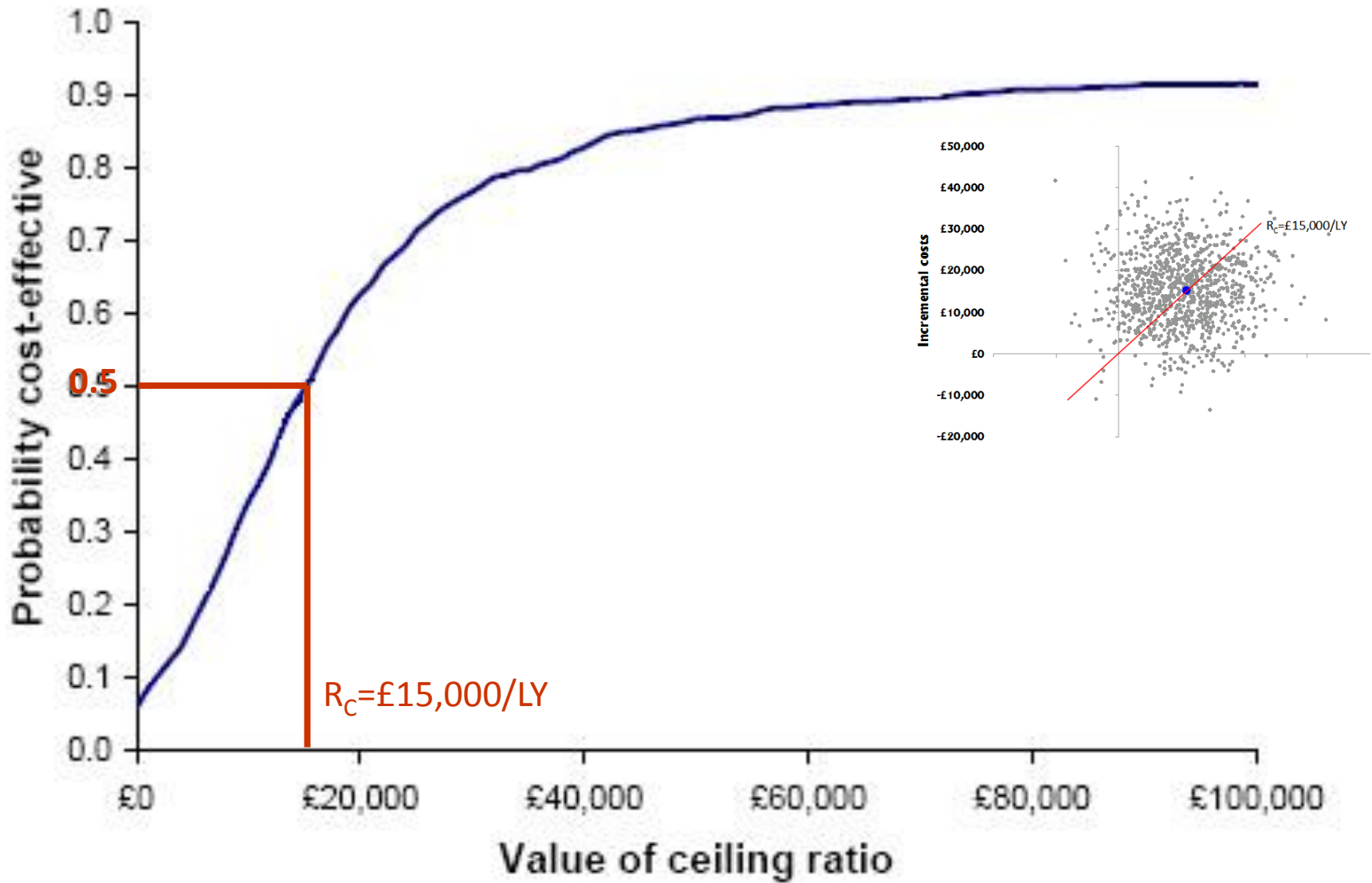
# Cost-effectiveness acceptability curves



Source: Briggs A (2004)

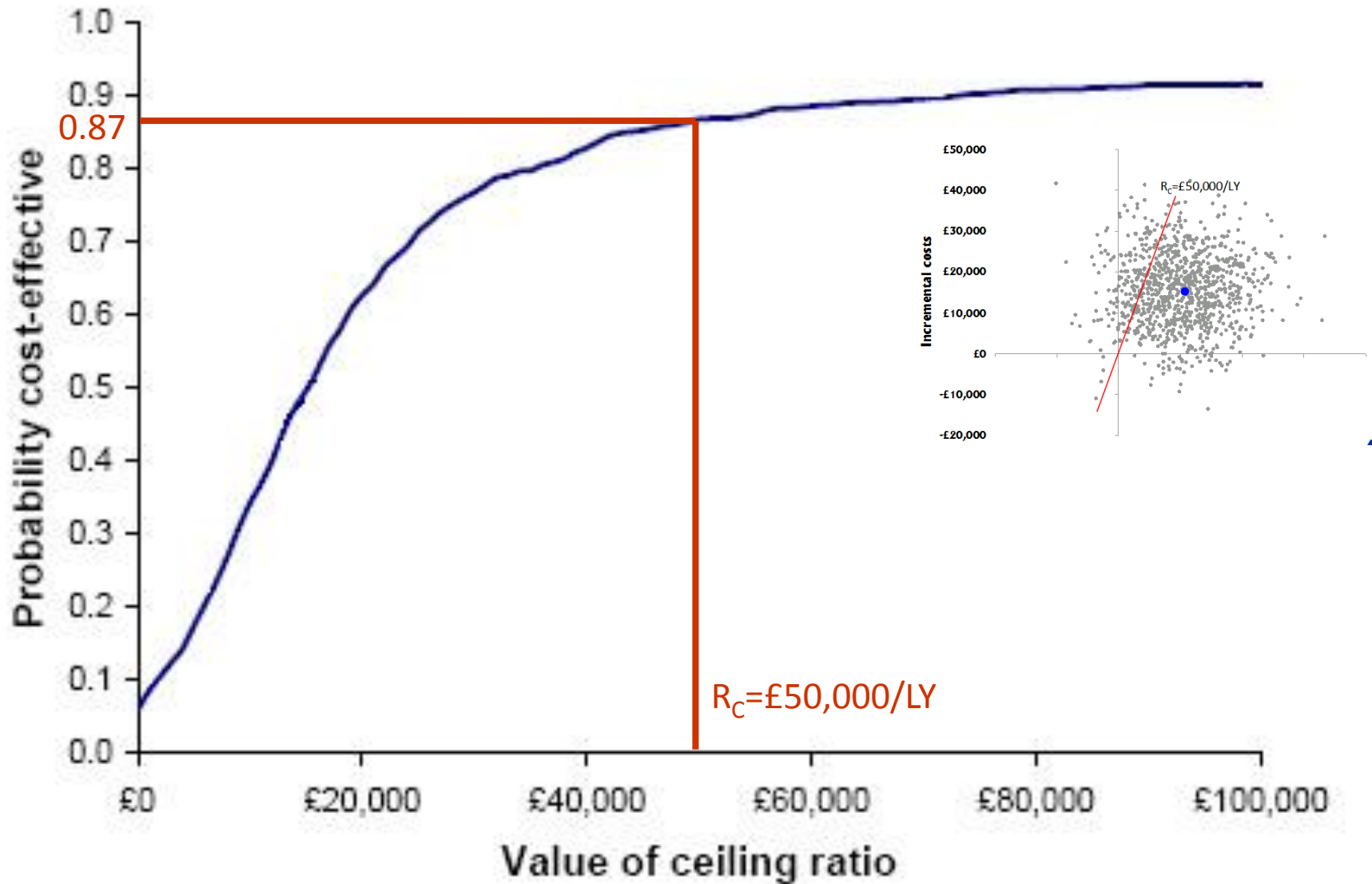


# Cost-effectiveness acceptability curves



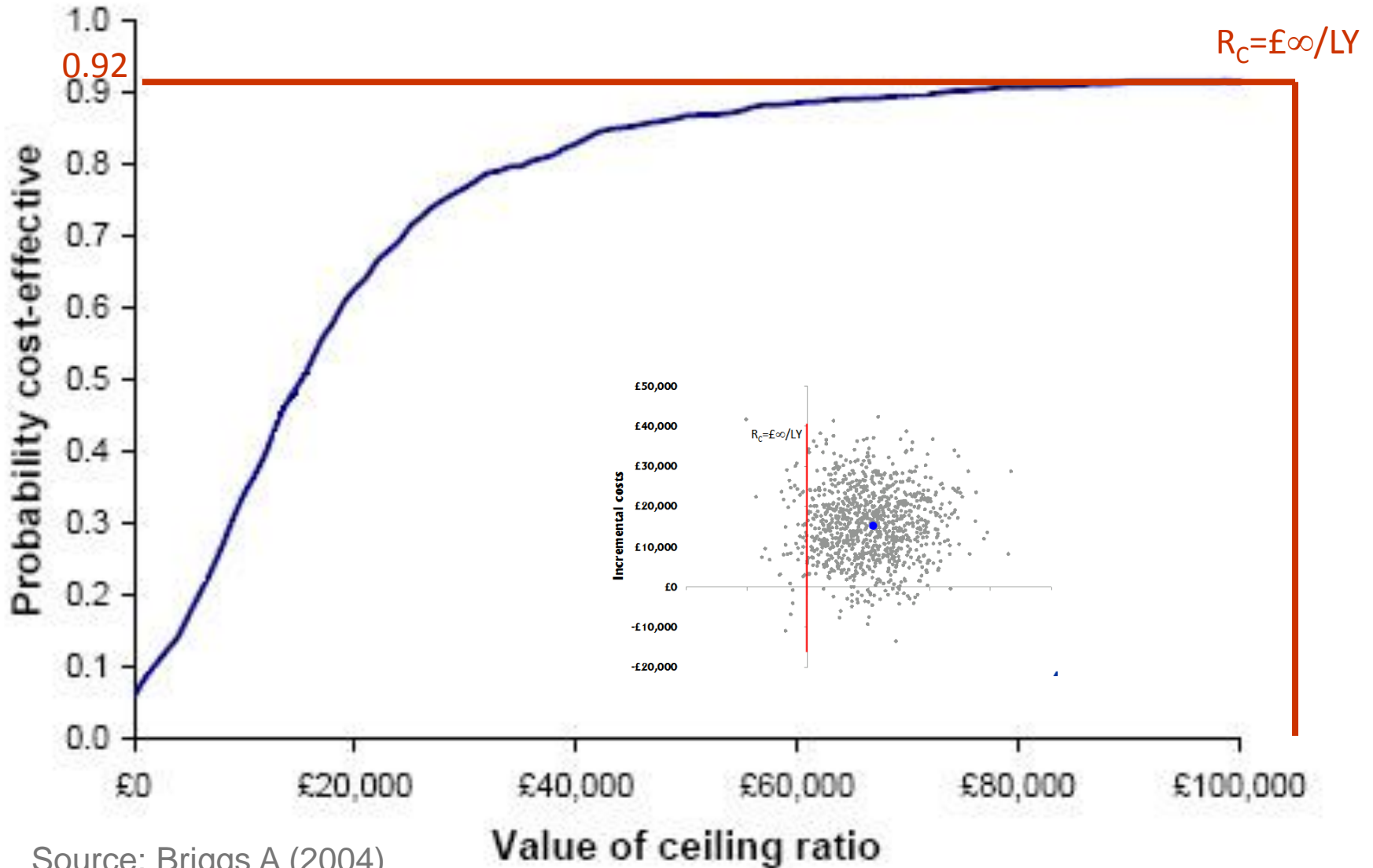
Source: Briggs A (2004)

# Cost-effectiveness acceptability curves



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# Cost-effectiveness acceptability curves



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# The need for multiple types of sensitivity analysis

- PSA is not the only sensitivity analysis that should be used
- Model structure and choice of data are also subject to uncertainty, which should be identified and formally examined using sensitivity analysis.
- This can be done by re-running analysis using alternative model assumptions or source of data (e.g. excluding a study from a meta-analysis) where there's doubt.
- Simple deterministic analysis can also help to validate models - does it behave as expected?
- Can also help to develop the decision makers' understanding of and confidence in the model.



# Generalisability / transferability

- “The extent to which the results of a study, as they apply to a particular patient population and/or a specific context, hold true for another population and/or in a different context” –Briggs and Gray 1999: <http://www.hta.ac.uk/fullmono/mon302.pdf>
- Clinical effectiveness *and* cost effectiveness
- Drummond et al 2009
  - “Generalisability” – economic evaluations applied with no ‘adjustment’
  - “Transferability” – adapted to apply in other settings
- Trial populations; Settings, etc
- Decision makers / analysts may need to consider data from alternative settings
  - How to interpret and use?



# Dealing with generalisability/ transferability

- Checklists – e.g. include / exclude studies
  - Qualitative assessment
- Quantitative approaches, e.g.
  - Regression analyses (if patient level data available)
  - Subgroup analysis
- Example: Briggs et al 2006 (cited in Drummond et al 2009)
  - Cost-effectiveness of asthma control: an economic appraisal of the GOAL study
  - used data from a multinational trial on baseline risks, relative treatment effects, utility, and resource use data
  - Regression analysis using data from the whole trial to estimate costs for just for United Kingdom
  - Assumed clinical / utility estimates generalisable across jurisdictions



Thankyou!

