The Use of a Probabilistic Sensitivity Analysis for Decision Making: The example of Drug-Eluting Stents

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Outline

- Rationale for probabilistic sensitivity analysis
- Overview of methods of PSA
- Case study – drug eluting stents

Policy background

- Cost-effectiveness analysis increasingly used for health service decision making
- Important role for decision modelling
  - Compare all relevant interventions
  - Synthesise available evidence
  - Extrapolation
  - Generalisation
- Decision models can identify:
  - Best option given available evidence
  - Probability of making the wrong decision
  - Value of additional research
- Part of the new NICE Reference Case

Uncertainty and variability

- Overall variability between patients
  - 1st order uncertainty
  - Reflected in standard deviations associated with a mean value
- Parameter uncertainty
  - 2nd order uncertainty
  - Uncertainty in mean parameter values
  - Reflected in standard error of the mean
- Sub-group heterogeneity
  - 'Base-line' characteristics 'explain' a proportion of overall variability between patients (e.g. age, sex)
  - Generate mean parameter values per sub-group
  - Variability *within* sub-group will remain
- Structural uncertainty
  - Uncertainty regarding modelling assumptions

Parameter uncertainty

Why probabilistic sensitivity analysis?

- Numerous parameters in decision models
- Each estimated with uncertainty
- Standard sensitivity analysis unwieldy
- Need to propagate joint parameter uncertainty in terms of decision uncertainty
- Quantification of decision uncertainty provides starting point for assessing the value of additional research
- In non-linear models, probabilistic models provide the only unbiased estimate of mean cost-effectiveness

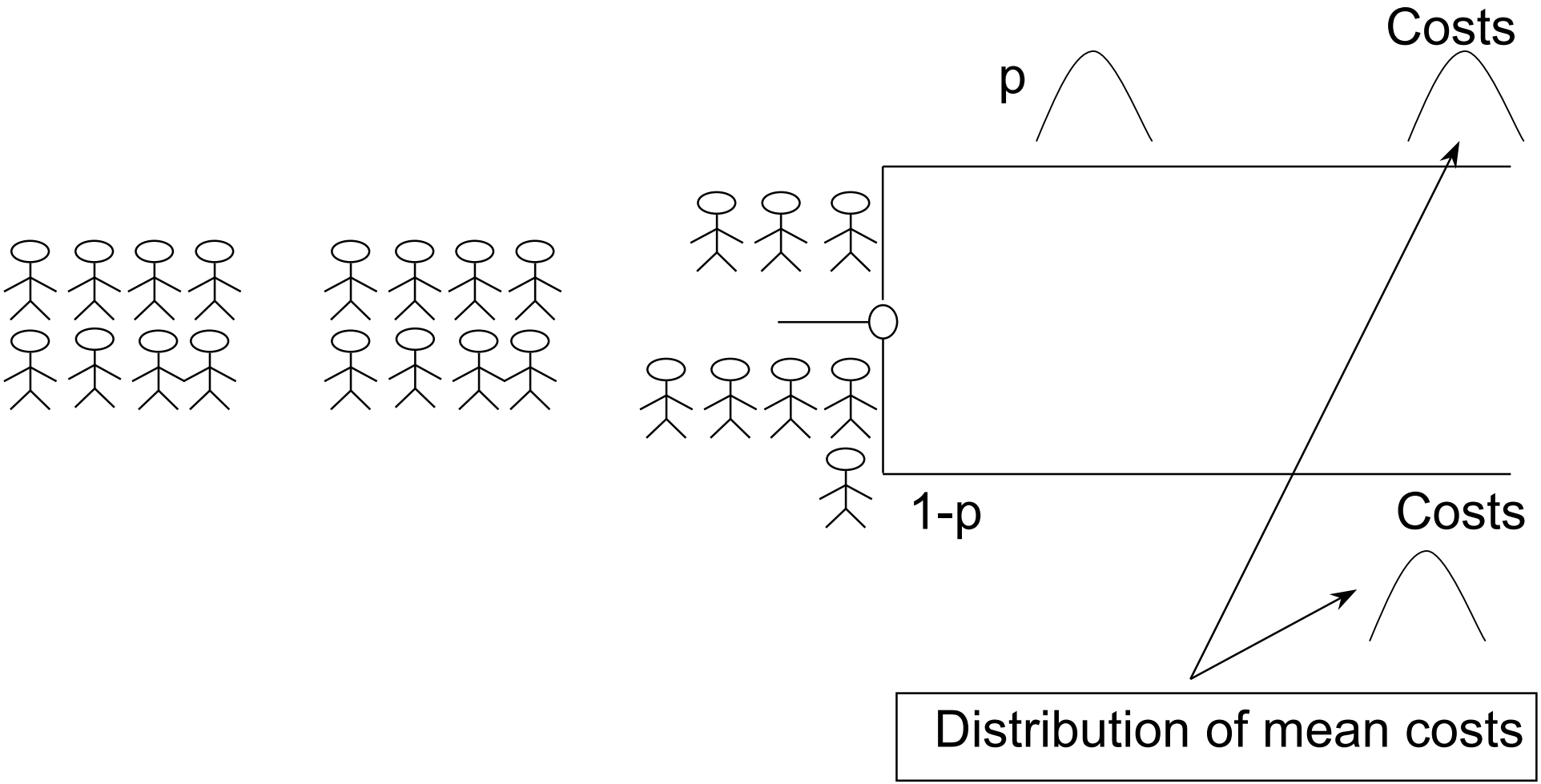
Probabilistic sensitivity analysis

Steps in the process

- Identify sources of parameter uncertainty
- Characterise uncertain parameters as probability distributions
- Define correlations as appropriate:
  - Patient-level data
  - Use of regression methods
- Propagate uncertainty through model using Monte Carlo simulation

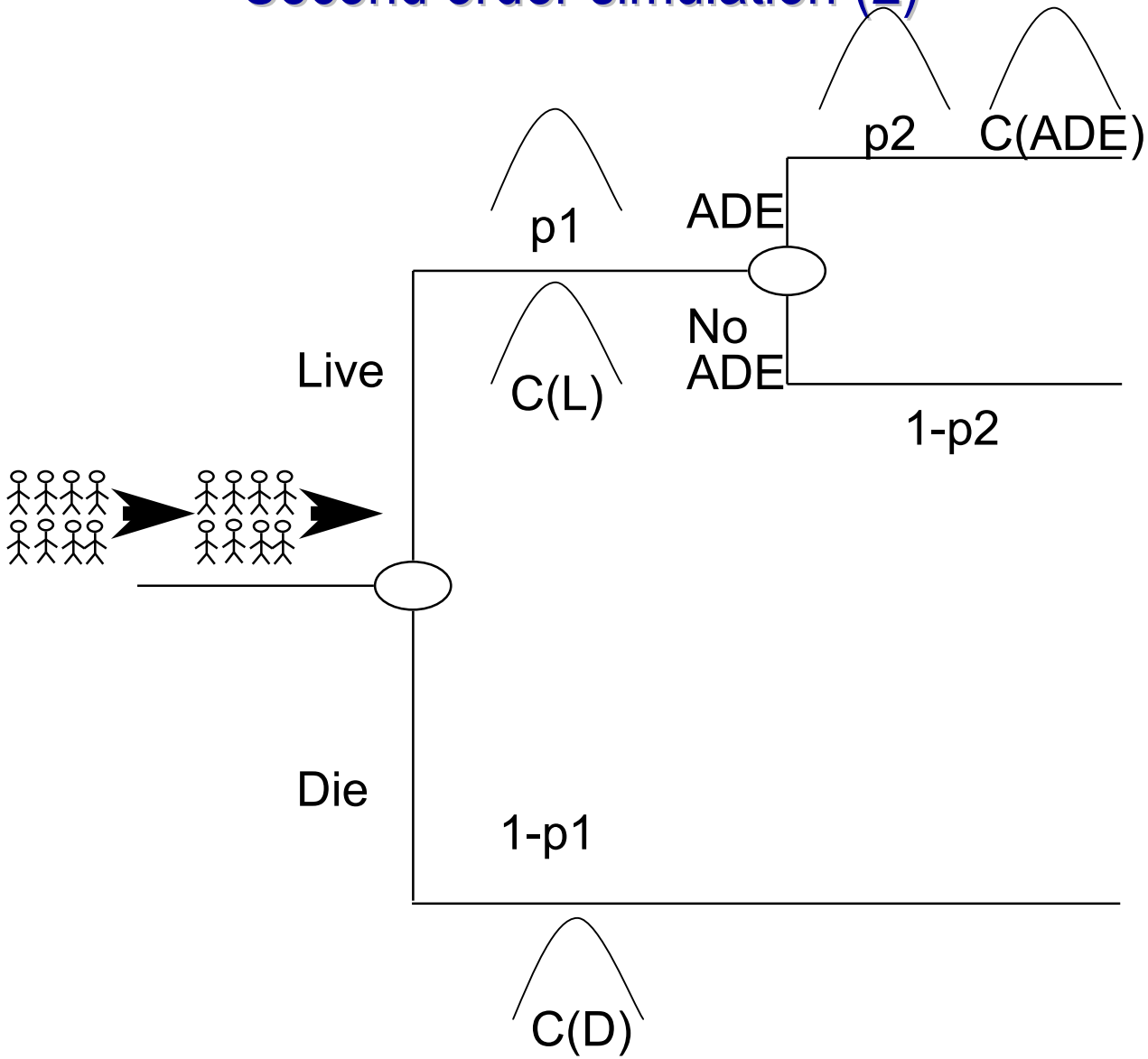
Monte Carlo simulation

Second order simulation (1)



Monte Carlo simulation

Second order simulation (2)



Costs: 300
Effects: 40

Costs: 220
Effects: 35

Costs: 420
Effects: 42

Costs: 380
Effects: 38

Costs: 250
Effects: 49

Costs: 290
Effects: 46

Costs: 350
Effects: 42

Selecting distributions

- Universe of possible distributions available
- Often criticised as arbitrary
- But choice for a given distribution is relatively small
- Parametric choices are frequently made in statistics

Selecting distributions

Commonly used distributions

Parameters	Distribution	Details
Probabilities	Beta	Between 0 and 1
Costs	Log-normal Gamma	Ranging from 0 to $\propto$
Utilities	Beta Gamma (1 – U)	Minus $\propto$ to 1
Relative risks	Log-normal	Ratios Additive on log scale

Case-study - background

- 2,100 deaths per million from coronary artery disease in UK – one of the highest in the world
- 1.4 million suffer from angina in the UK
- Percutaneous coronary interventions (PCI) provide a major therapeutic option in patients resistant to medical therapy
- About 85% of PCIs now undertaken using coronary stents in the UK
- Restenosis is a common problem with PCI
- Drug eluting stents have been shown to reduce restenosis
- Can their acquisition cost be justified?

Case-study - objectives

- To assess the cost-effectiveness of sirolimus-eluting stent (CYPHER™) compared to bare metal stents
- Based on treatment effects taken from three randomised trials
- Express health benefits in terms of quality-adjusted life-years
- Assess variation in cost-effectiveness by patient characteristics
- Use probabilistic sensitivity analysis to assess decision uncertainty

Key methods

- Base-case assumption of no differential effect on mortality
- QALY decrement through restenosis: symptomatic time waiting for further revascularisation
- Time horizon of 12 months based on trial follow-up
- Health service (payer) perspective

Source of data on treatment effects

Trial characteristic	Ravel	E-SIRIUS	SIRIUS
Sample size	238	352	1058
Diabetes mellitus (%)	19	23	26
Multi-vessel disease (%)	30	36	42
Reference vessel diameter (mm, mean ± SD)	2.62 ± 0.53	2.55 ± 0.37	2.80 ± 0.47
Length of lesion (mm, mean ± SD)	9.58 ± 3.25	15.0 ± 6.0	14.4 ± 5.8

Key data inputs – treatment effects

Input	RAVEL		E-SIRIUS		SIRIUS	
	Sirolimus	**Bare metal**	**Sirolimus**	**Bare metal**	**Sirolimus**	**Bare metal**
Further procedures (target lesions)						
- PCI	1/120 (0.008)	18/118 (0.153)	8/175 (0.046)	42/177 (0.237)	40/533 (0.075)	130/525 (0.248)
- CABG	1/120 (0.008)	0/118 (0.000)	1/175 (0.006)	4/177 (0.023)	8/533 (0.015)	16/525 (0.030)
MI	4/120 (0.033)	6/118 (0.051)	8/175 (0.046)	4/177 (0.023)	16/533 (0.030)	18/525 (0.034)

Other key data inputs

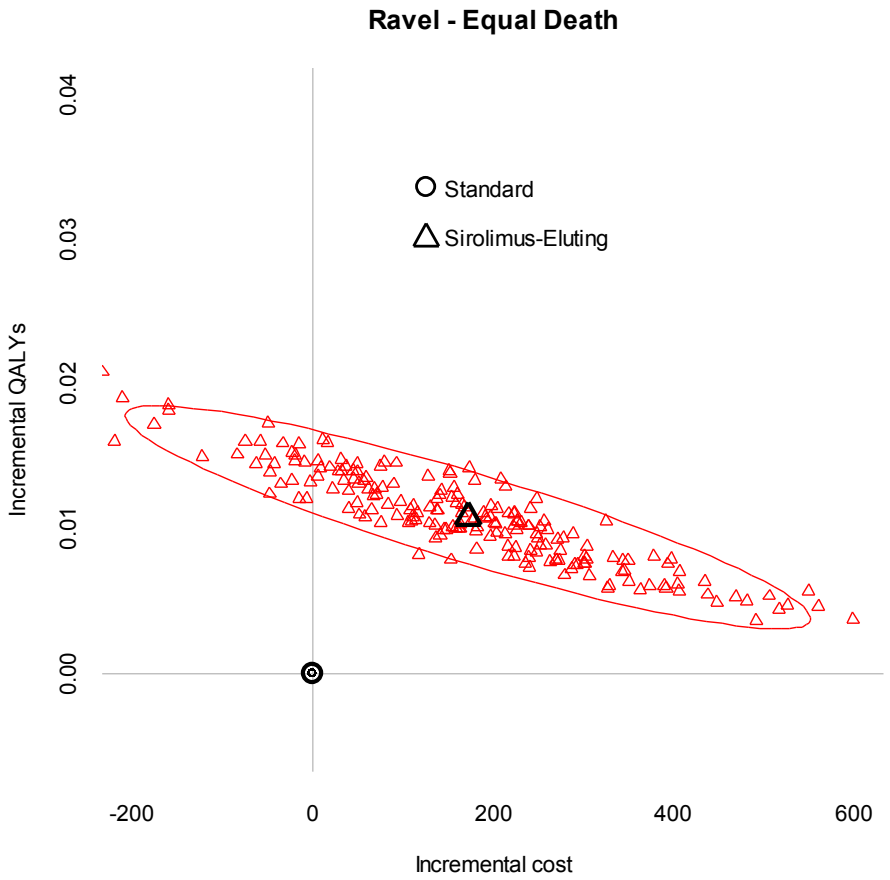
Input	Value
Cost of Sirolimus-eluting stent	£1,762
Cost of bare metal stent	£1,145
Cost of PCI	£2,984
Cost of CABG	£6,450
Utility without symptoms	0.84 ± 0.16
Utility with symptoms	0.69 ± 0.20
Waiting times for revascularisation (Days)	196

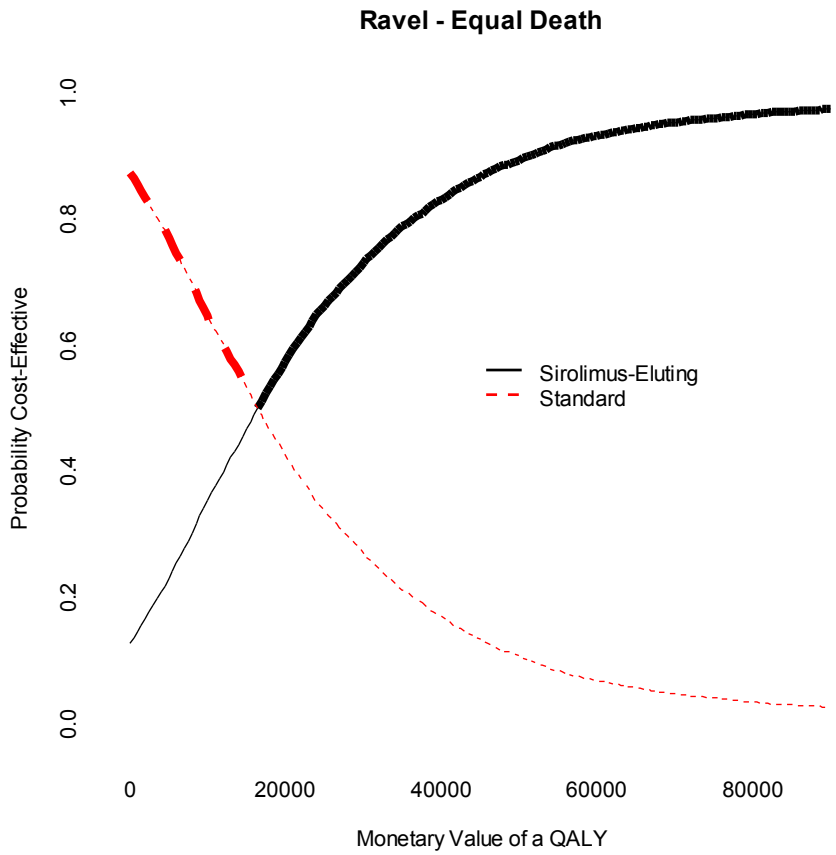
Base-case results

Input	RAVEL	E-SIRIUS	SIRIUS
Difference in costs	£166	£53	£113
Difference in QALYs	0.011	0.017	0.015
ICER	£15,198	£3,181	£7,461

Probabilistic sensitivity analysis

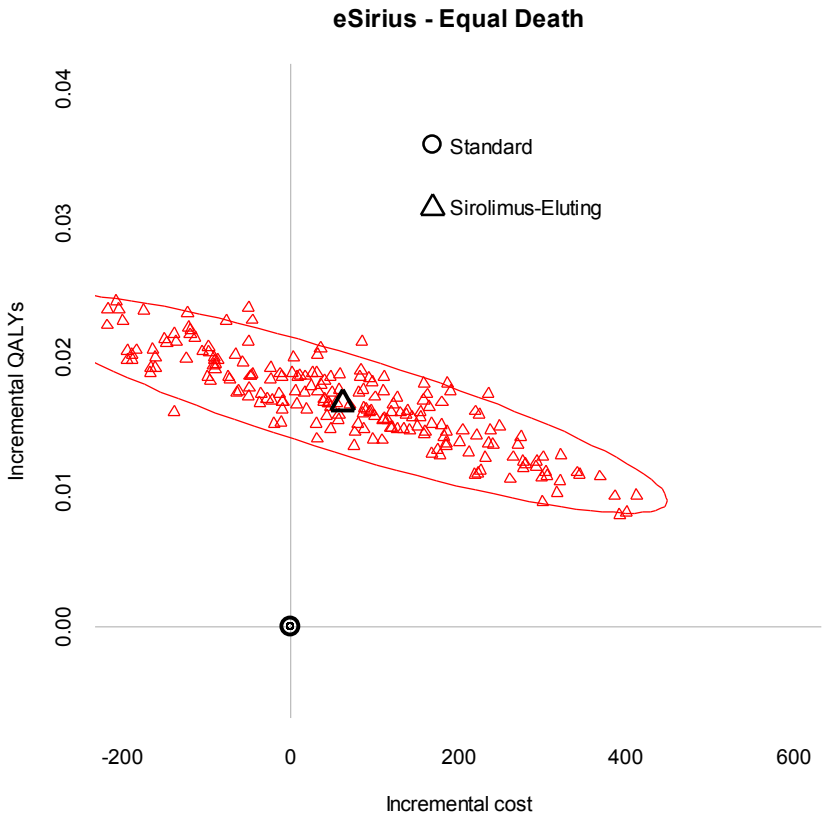
RAVEL Trial

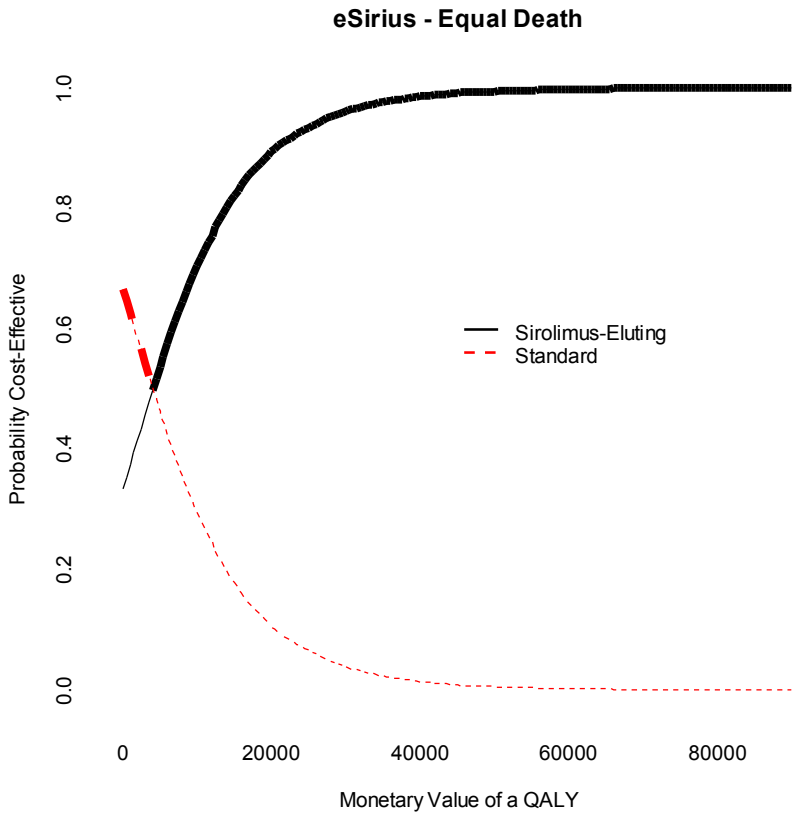




Probabilistic sensitivity analysis

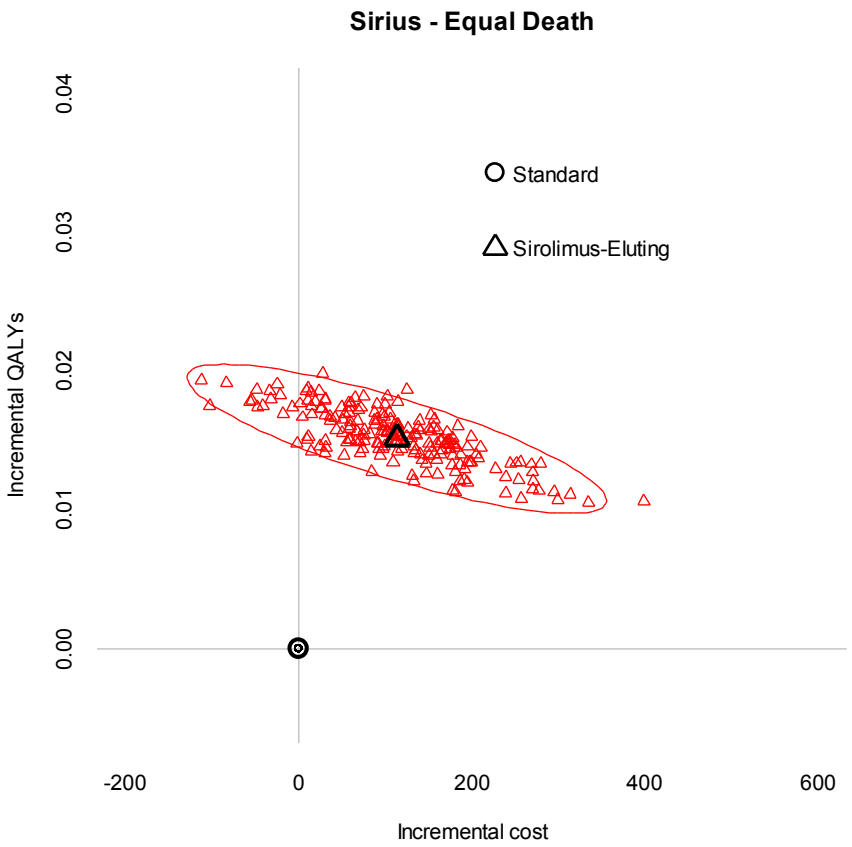
E-SIRIUS Trial

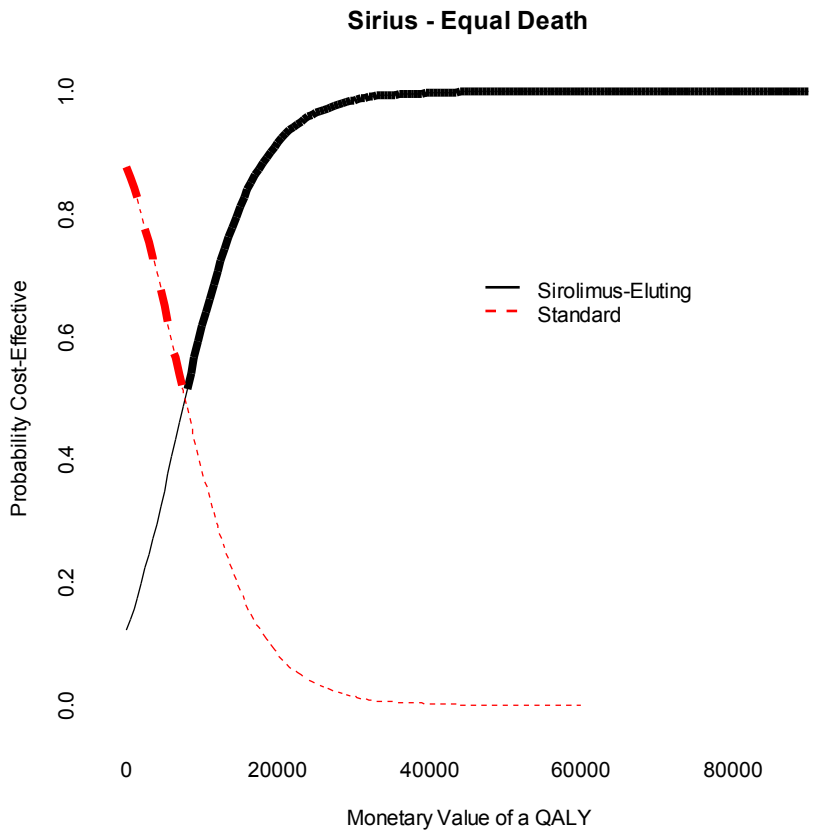




Probabilistic sensitivity analysis

SIRIUS Trial

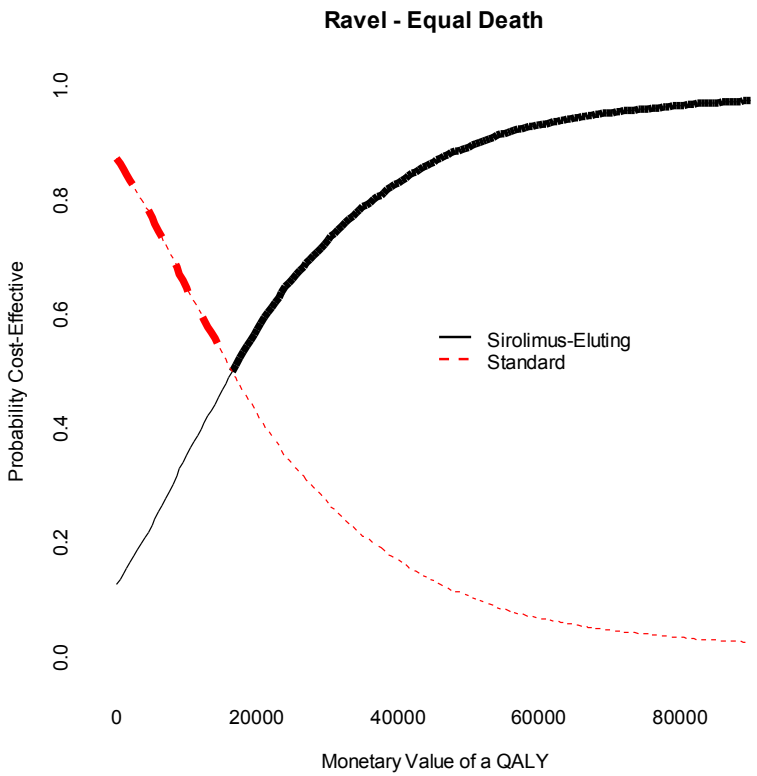




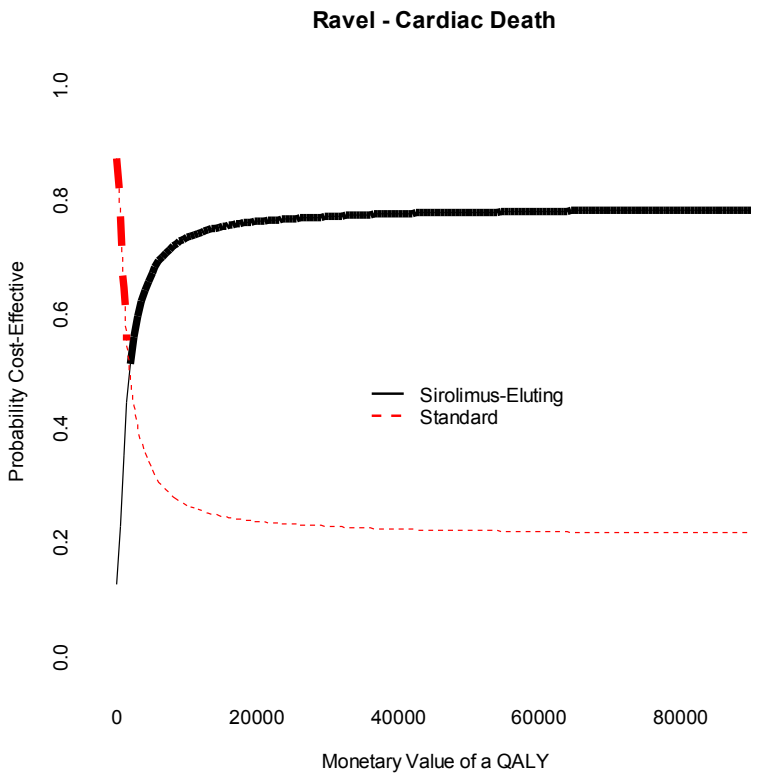
Further sub-group analysis

Sub-Groups	ICERs
Sub-group 1	
Diabetics	£2,848
Non-diabetics	£10,432
Sub-group 2	
Long lesions	£30,864
Non-long lesions	DES dominates
Sub-group 3	
Small vessel disease	£5,569
Non-small vessel disease	£8,746

Alternative assumptions about mortality



ICER = £15,198



ICER = £1,674

Conclusions

- Based on 12-month trial data, reduction in restenosis results in cost offset to acquisition of DES
- Reduction in restenosis has a impact of quality of life
- Waiting times for procedures one way to capture these effects
- DES appears cost-effective based on standard NICE thresholds
- Decision uncertainty: 0.8 to 0.42 depending on trial and assuming equal mortality
- ICERs (and uncertainty) sensitive to assumptions about mortality