Stratified Cost-Effectiveness Analysis
(with implications for sub-group analysis)
(and applications to value-based pricing)

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Stratified CEA: Overview

- Standard approach to CEA in clinical trials
- The importance of sub group analysis
- Example 1:
  Cost-effectiveness of statins (HPS)
- Example 2:
  Cost-effectiveness of ACE-inhibitors (EUROPA)
- Application to Value-Based Pricing

Standard approach to CEA alongside clinical trials

Well established, but not without issues:

- Examines overall CEA in trials
- Ignores potential heterogeneity
  - Subgroups potentially important
  - ‘Splitting’ data not optimal
- CEA can lack power
  - Sample size based on effectiveness only
  - High variance of cost data

Components of cost and effect

Components of incremental cost

$$\Delta C = \Delta C_{Rx} + \Delta C_{SE} - \Delta C_{Morb} + \Delta C_{\Delta LE}$$

Components of incremental effectiveness

$$\Delta E = \Delta E_{LE} + \Delta E_{Morb} - \Delta E_{SE}$$

Weinstein & Stason, 1977

Statistical modelling of the components of the CEA calculus

Offers some potential advantages:

- Can choose appropriate statistical model for component
- Can vary explanatory variables by component
- Allows different scales for different components
- Can address sub-group analyses while avoids splitting the data
- Can form the basis of extrapolation
- Easier to incorporate additional/external evidence

Statistical modelling of the components of the CEA calculus

Potential problems:

- Too much ‘structure’ to the analysis
- Results are conditional on the assumptions holding

Example 1: Multivariate range of risk (5-year MVE risk) in Heart Protection Study

	Quintiles of vascular risk				
Multivariate*	12%	18%	22%	28%	42%

*Cox proportional hazards model estimates the 5-year risk of MVE with baseline prior vascular disease or diabetes, age, sex, LDl and HDL cholesterol, midpoint of SBP and DBP, smoking status, creatinine and statin allocation as covariates.

HPS collaborative group, *The Lancet*, 2005

Assessing subgroup effects reliably

- Analyses in different subgroups indicate:
  - Similar relative reduction in vascular events
  - Similar relative reduction in costs of vascular events
  - Similar absolute difference in statin treatment cost
- Hence, cost-effectiveness for subgroups estimated by applying overall treatment effects to placebo event rates and costs observed in each subgroup

Within subgroup and constant relative/absolute impact

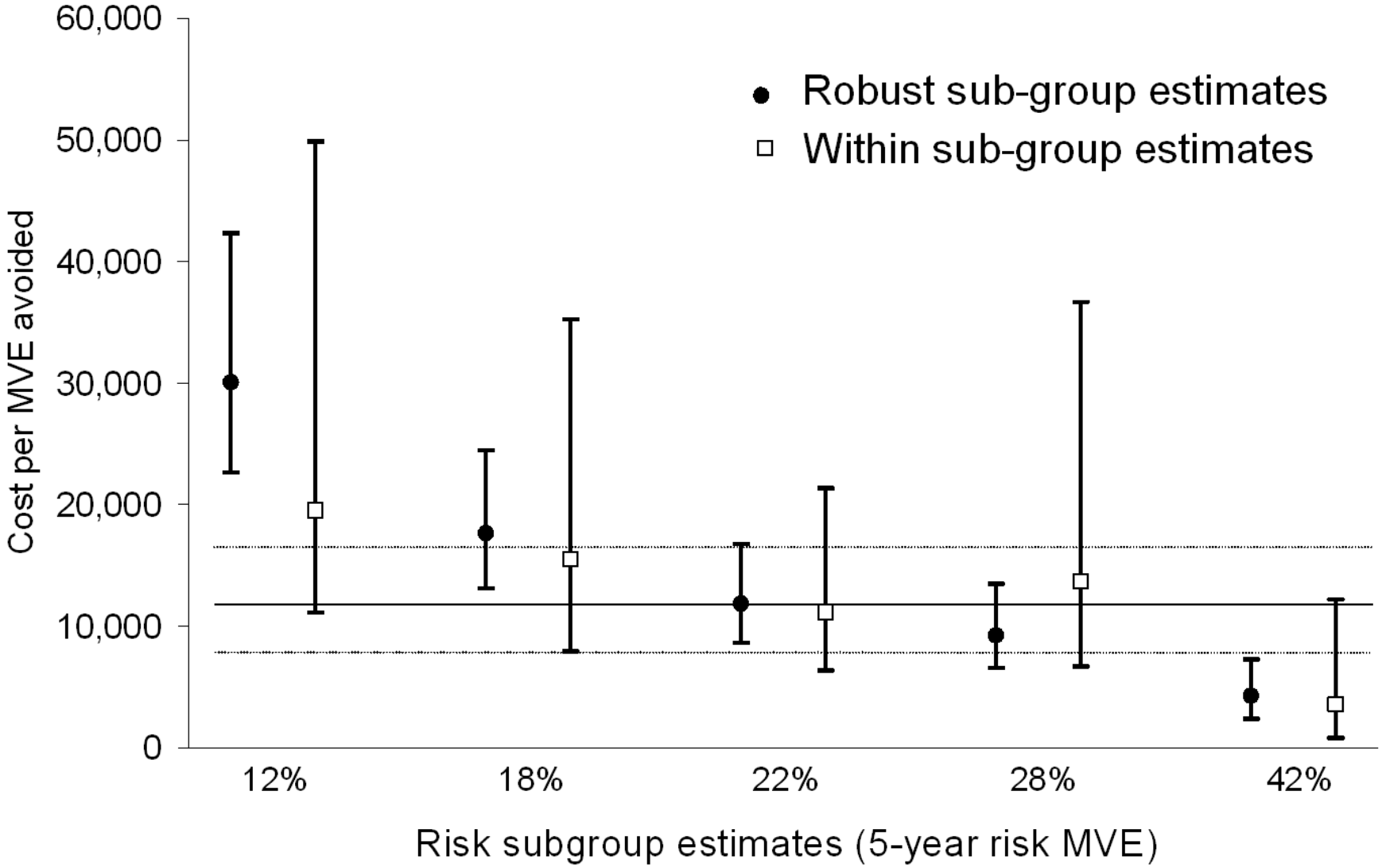


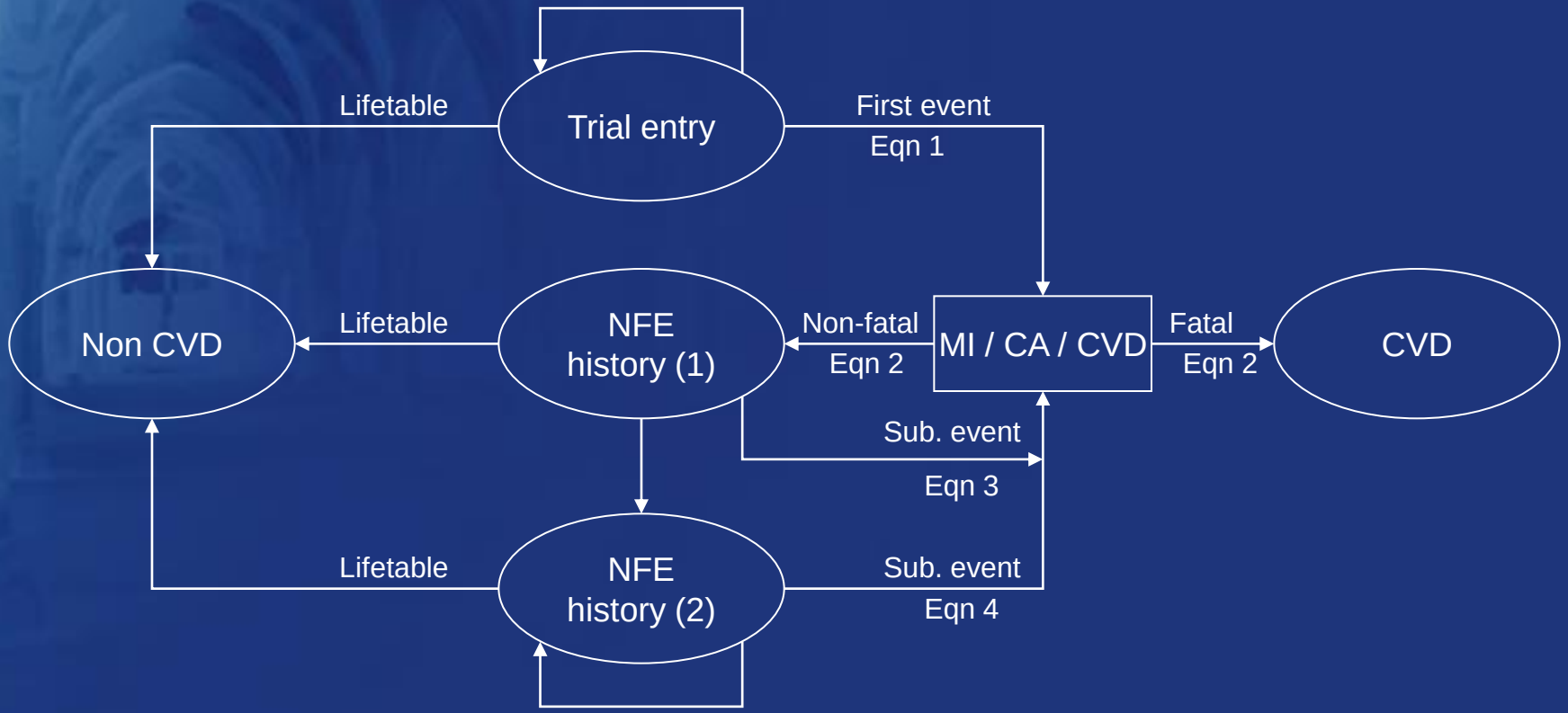
Illustration: Economic analysis of the EUROPA study from the UK perspective

EUROPA trial

- Multi country trial of ACE-inhibitor for prevention of cardiovascular disease
- 12,000+ patients randomised to ACE-I or placebo and followed for mean of 4.2 years
- Clinical trial showed 20% reduction in primary (composite) endpoint of CV death or non-fatal MI/cardiac arrest

EUROPA investigators, *The Lancet*, 2003
Briggs et al, *Heart*, 2007

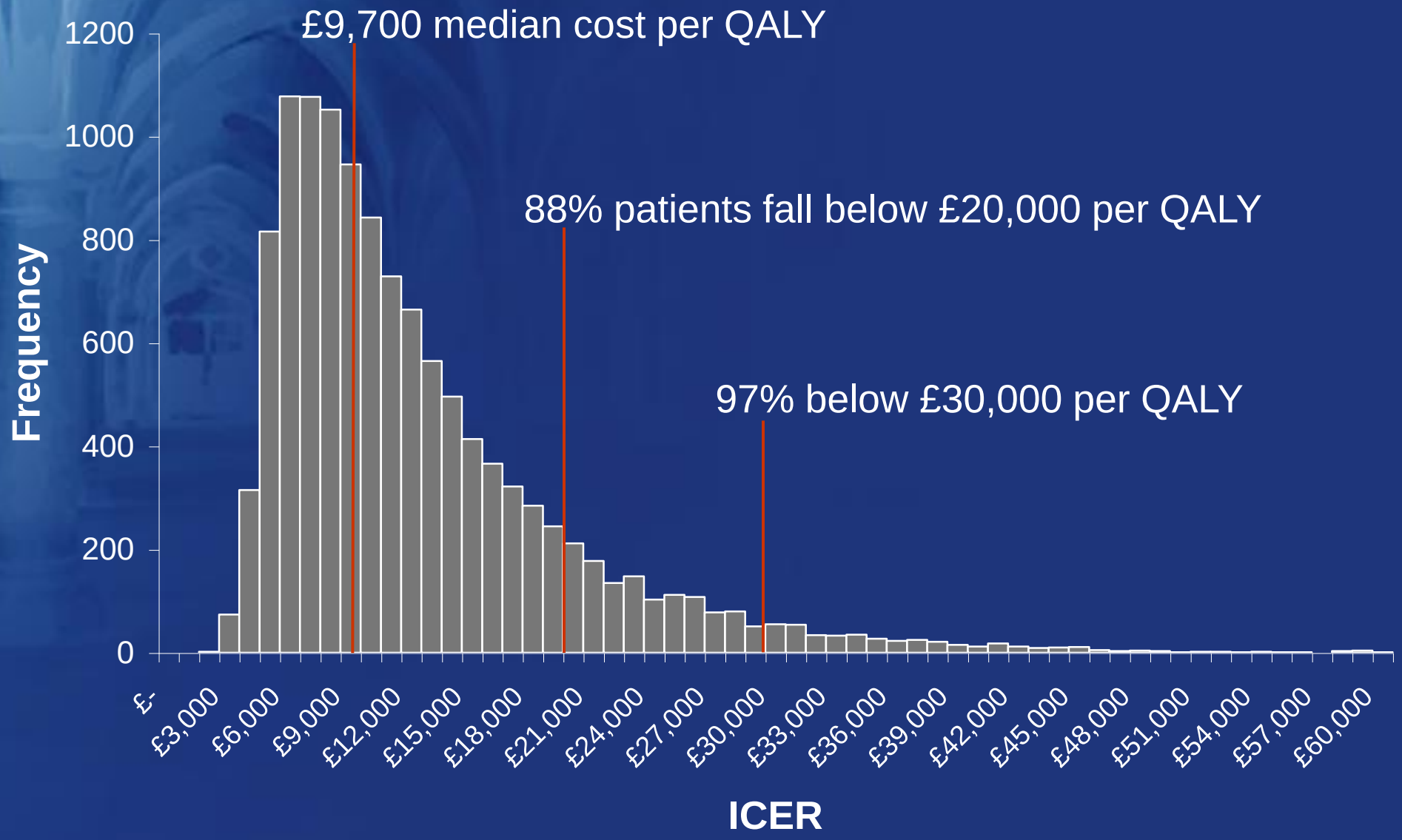
Event-based model of EUROPA



Explanatory variables to model heterogeneity

- Rx group
- Age
- Gender
- Smoking
- Previous MI
- Revascularisation
- Vascular disease
- Diabetes
- Family history
- Angina
- Blood pressure
- Kidney function
- Cholesterol
- Obesity
- Taking beta blockers
- Taking statins
- Taking nitrates

‘Individualised’ subgroups in EUROPA
Cost-effectiveness for all covariate patterns



OFFICE OF FAIR TRADING

The Pharmaceutical Price Regulation Scheme

An OFT market study

Key recommendations

- **We recommend that Government reform the PPRS, replacing current profit and price controls with a value-based approach to pricing**, which would ensure the price of drugs reflect their clinical and therapeutic value to patients and the broader NHS.
- We believe this would provide **major benefits to patients and innovative companies** in the short and long term:
  - **value for money for the NHS:** we have identified hundreds of millions of pounds of expenditure per year that could be used more cost effectively under value-based pricing, allowing patients greater access to drugs and other healthcare benefits they are currently being denied. In short, the same level of expenditure could be used to produce greater benefits for patients.
  - **better incentives to invest:** more value-reflective prices would give companies much stronger incentives to invest in the drugs that are most beneficial to society, particularly in areas of unmet patient need. Given the international importance of UK prices, these benefits would be felt not just in the UK, but globally.
  - **a stable, sustainable system:** these reforms would improve stability for Government and industry in the long run, by avoiding reliance on increasingly arbitrary profit and price controls and ensuring instead that future pricing decisions are based on an informed, rational debate about how to make the best use of available NHS resources.
- International experience shows that value-based pricing can work well in countries that have fewer resources than we enjoy in the UK but companies have highlighted key issues that need to be addressed in ensuring effective implementation. We believe we have met these concerns in developing options for reform that will provide **a credible, practical pricing regime for the long term**.

How would VBP work?

- Links price NHS will pay to value drug provides
- This creates the appropriate incentives for value for NHS
- Appears reasonable, but ‘devil is in the detail’
- Pharmaceutical industry have objected
  - but dangers too for the NHS
- Focus here on what this means for ‘sub-group analysis’ in cost-effectiveness studies

But what if price had not been set and company faces VBP?

- What are the incentives to the company?
  - To employ ‘average’ pricing for patient group
  - Effectively ‘hiding’ heterogeneity in value to gain full benefit from NHS
- What are the dangers to the NHS?
  - Effectively lose ‘consumer surplus’
  - Drug has zero value to NHS
- What is the solution?
  - Careful subgroup analysis
  - ‘Signalling’ NHS demand curve

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Weinstein & Stason, 1977

Manipulating the cost-effectiveness decision rule

- Recall $ICER = \frac{\Delta C}{\Delta E}$
- Decision rule: $ICER < \lambda$ then implement
- Net-benefit: $NMB = \lambda \cdot \Delta E - \Delta C$
- Recall: $\Delta C = \Delta C_{Rx} + \Delta C_{SE} - \Delta C_{Morb} + \Delta C_{\Delta LE}$
- Value: $V = \lambda \cdot \Delta E - \Delta C_{SE} - \Delta C_{Morb} + \Delta C_{\Delta LE}$

Industry incentive: price at average value

- Calculate average value across whole trial:

$$V = \lambda \cdot \Delta E - \Delta C_{SE} - \Delta C_{Morb} + \Delta C_{\Delta LE}$$

- In EUROPA this is:
  - £1,758 for five-years of treatment
  - £26.98 per 28 day pack supply

- Therefore £25.00 pricing is ‘cost-effective’ with ICER < £30,000 per QALY

Steps to generating a ‘demand curve’ for ACE-Inhibitors based on EUROPA trial

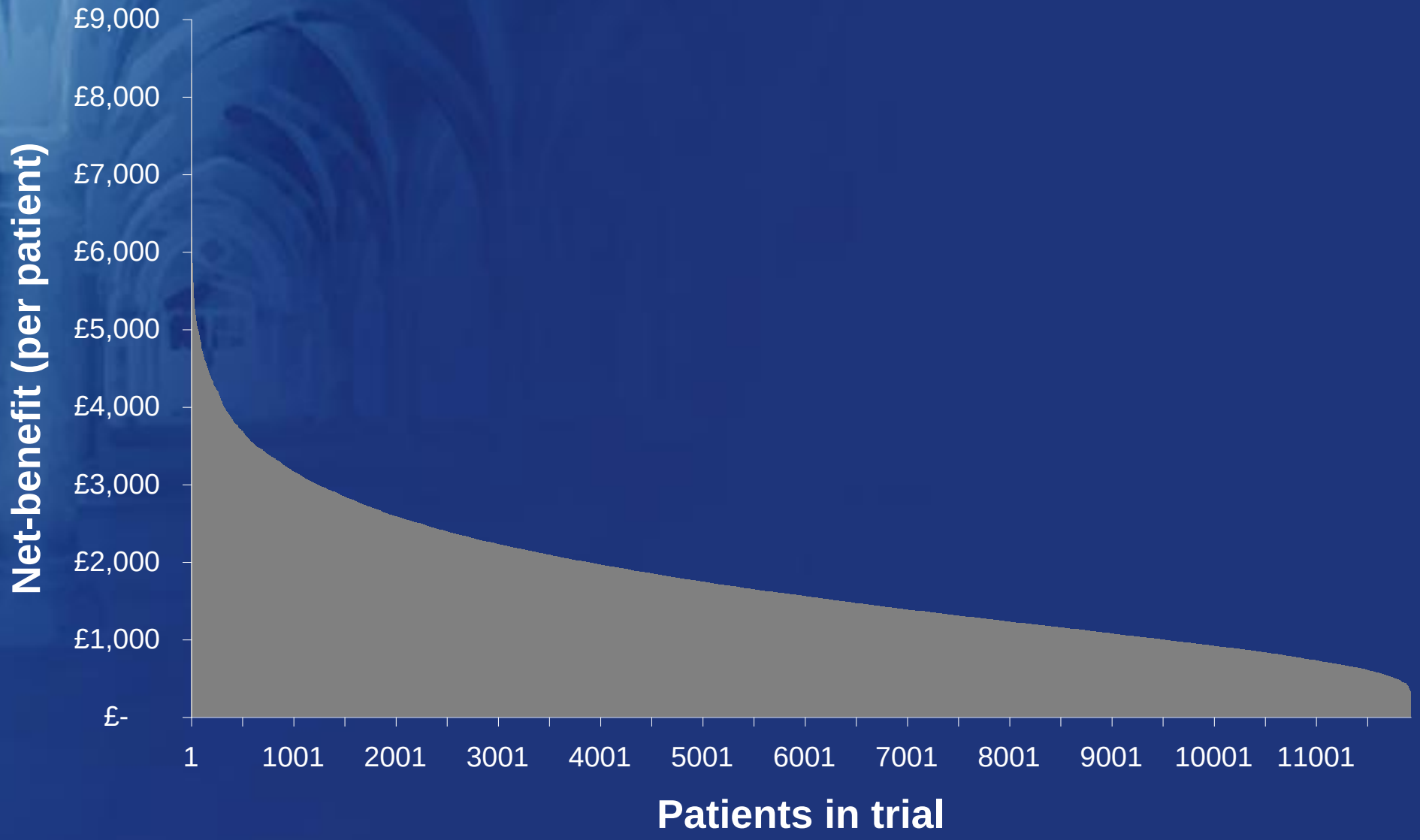
- For each patient calculate

$$V = \lambda \cdot \Delta E - \Delta C_{SE} - \Delta C_{Morb} + \Delta C_{\Delta LE}$$

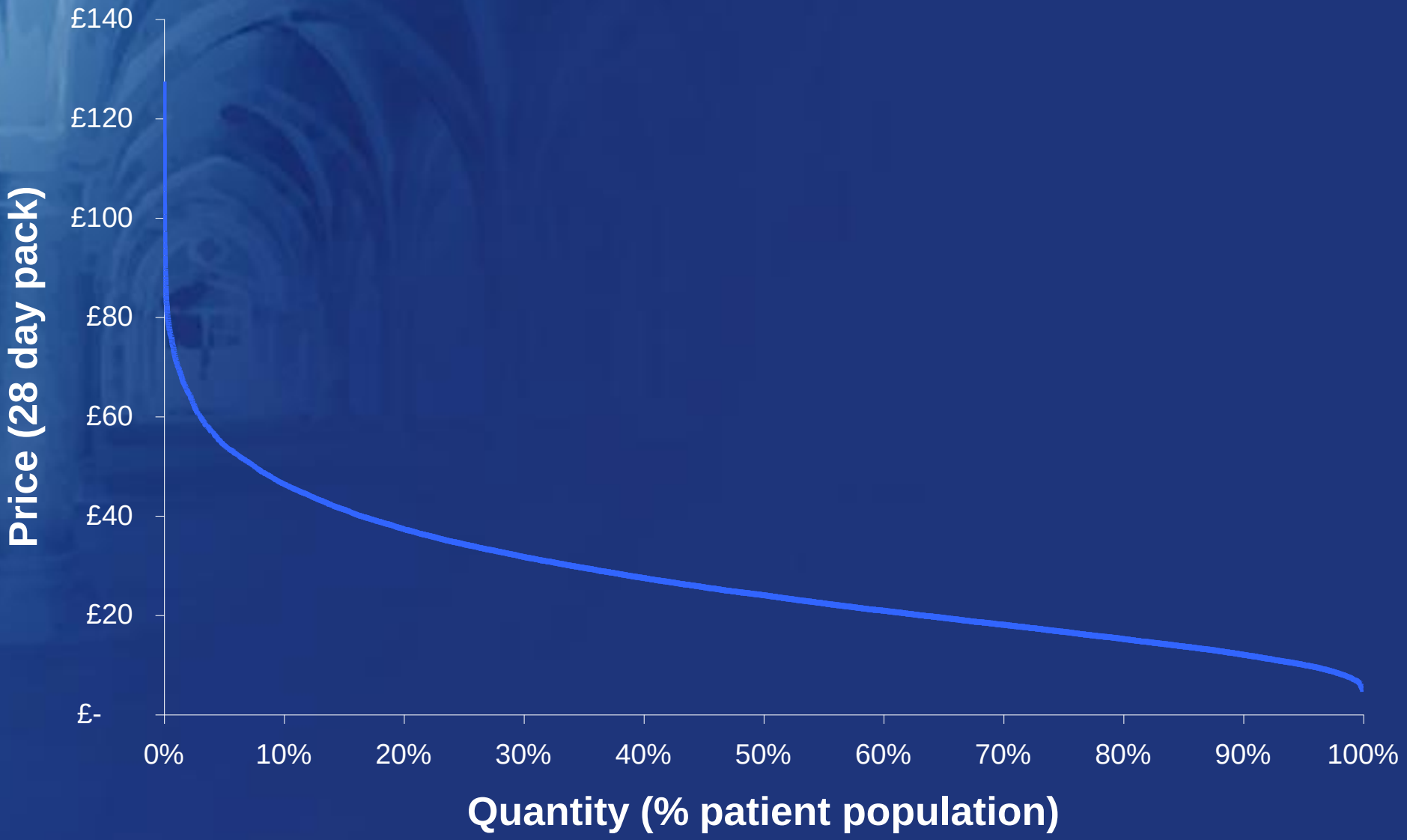
(that is the value excluding drug cost)

- Rank order by this value
- Plot for each patient

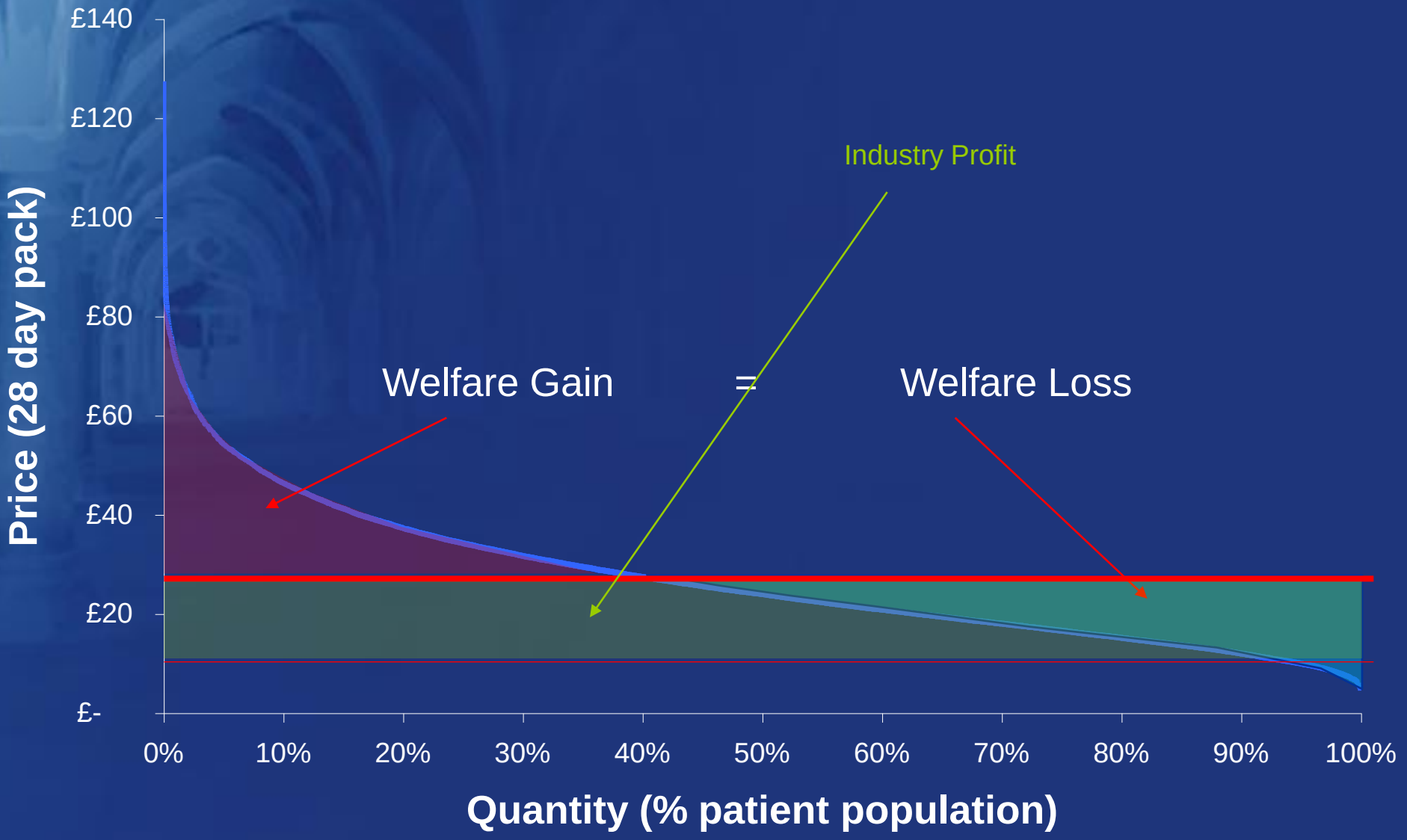
Plotting net-benefit for EUROPA



Demand curve



Industry pricing at average value



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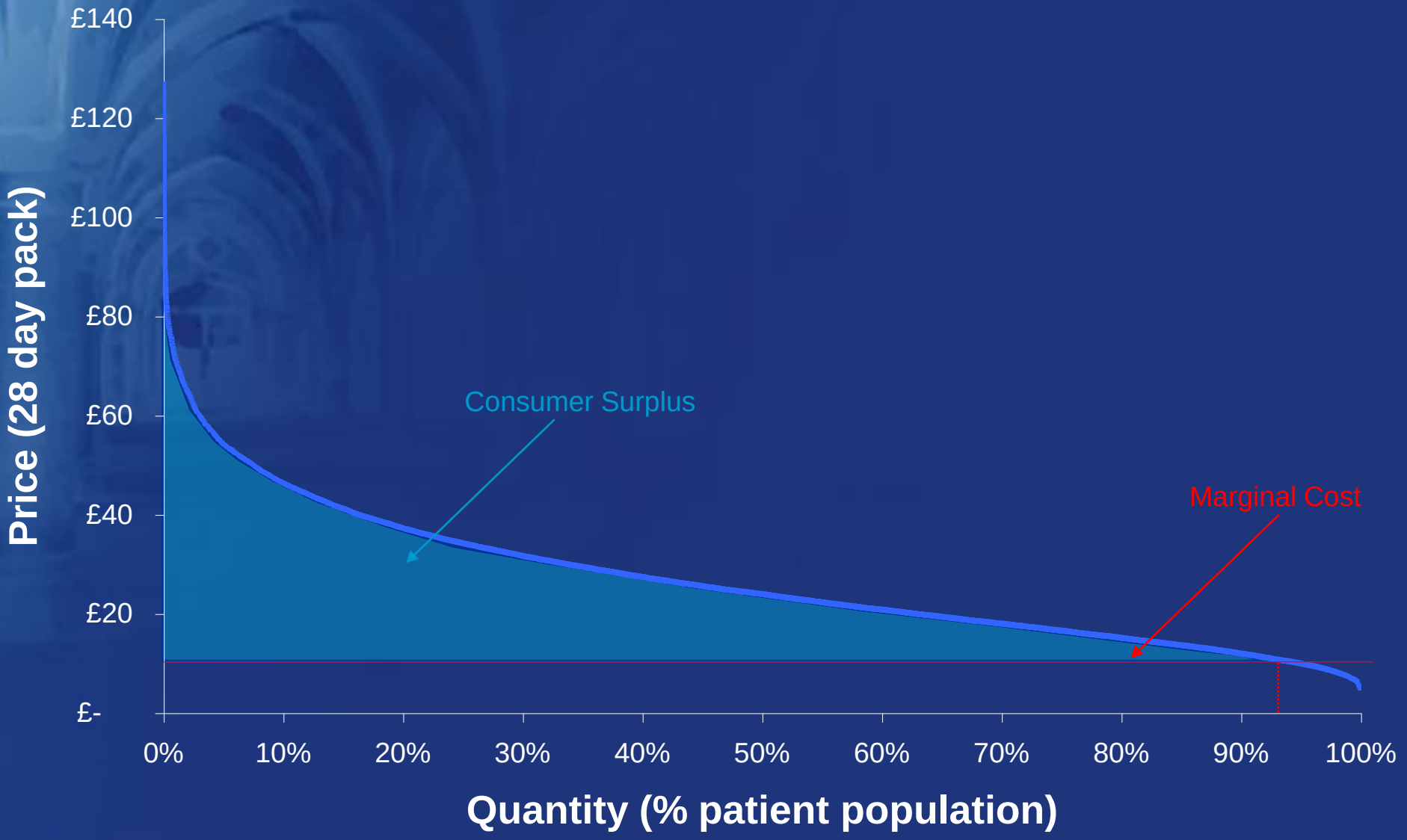

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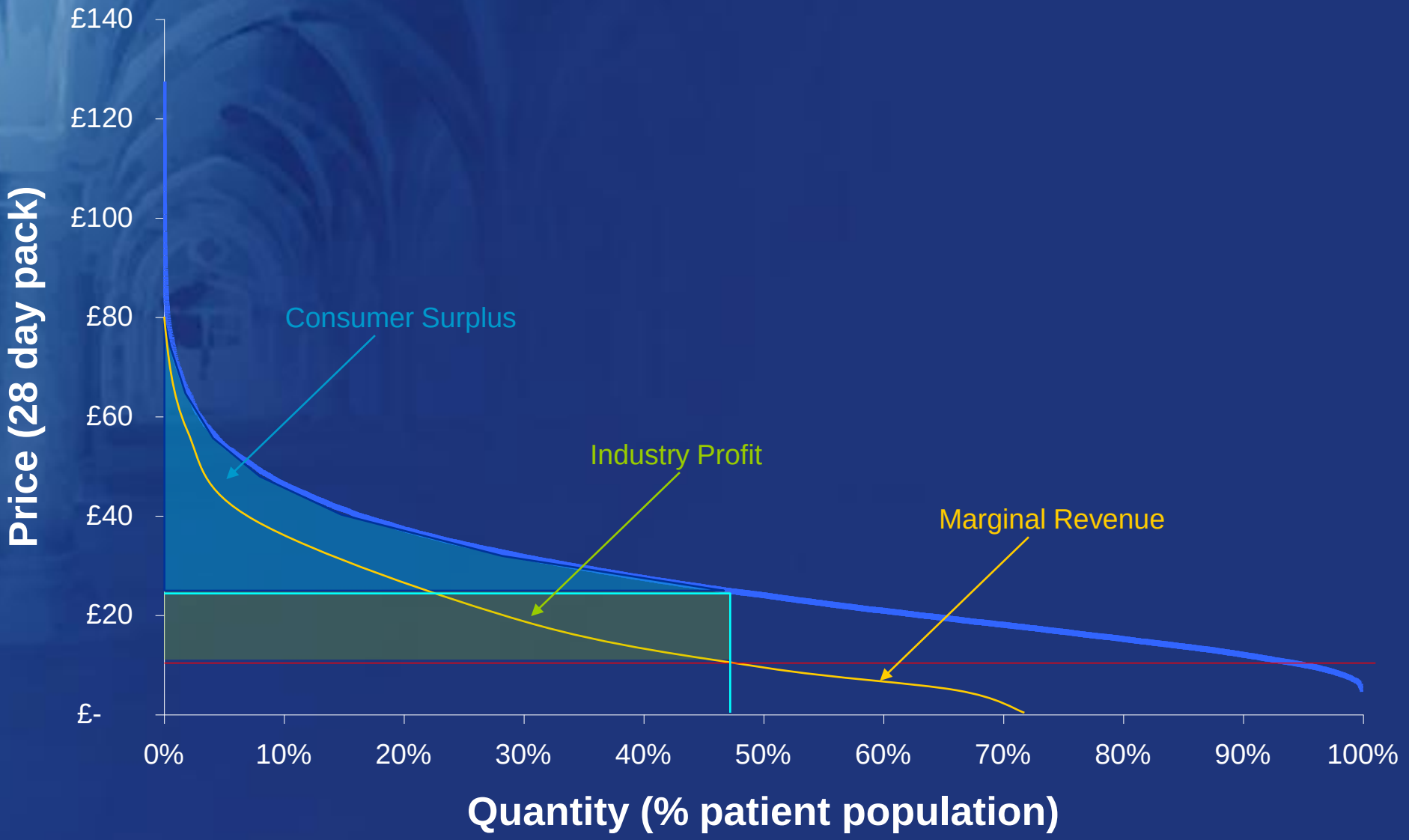

Could VBP work?

- Industry incentive: price at average value
- NHS incentive: squeeze marginal cost pricing
- Solution?
  - Signal demand curve
  - Allow monopoly pricing for patent period
- Can only be achieved with careful analysis

Conclusions

- Reimbursement policy fundamentally interested in sub-groups / heterogeneity in CEA
- Standard approaches to CEA in trials
  - Often underpowered
  - Average over heterogeneity
- Statistical modelling of trial events make full use of available patient-level
  - Robust subgroup analysis
  - Offer increased precision
- Value-based pricing is likely to increase the interest in stratified CEA