NEGOTIATING PRICE AND DATA IN AN ERA OF CONDITIONAL APPROVAL: “STICK” OR “TWIST”?

Project Context

Warren Cowell

Market Access Policy, Janssen (UK)

The new CDF in UK

- Implications of coverage with evidence development; theoretical consequences and practical considerations

- Increasingly relevant issue
  - Adaptive regulatory licensing
  - HTA evidence more uncertain due to earlier timelines, evolving evidence bases
  - Appraisal resourcing and proportionality

Caveat: personal views, rather than formal Janssen/industry positions

The new CDF

- NICE can now issue conditional approval, when a new medicine is promising but the evidence is limited
  - The ICER range must span NICE's threshold
  - The Appraisal Committee's 'most plausible' ICER (mpICER) should be above the threshold
  - Uncertainty expected around estimates for mean OS improvement, real world outcomes
- With conditional approval ('twist')
  - Evidence generation plan
  - Interim reimbursement agreement
  - Subsequent NICE re-appraisal (and reimbursement accordingly)
- Without ('stick')
  - Discount sufficient to bring mpICER below the threshold

Alternative possible ‘truths’

- The true ICER is better/same/worse compared to NICE’s initial mpICER
- Why might it be the same?
  - (NICE’s) economic modelling is accurate
  - Any inaccuracies are negligible, or cancel out
- Why might it be better?
  - If NICE’s most plausible estimate is actually conservative
  - E.g. most plausible might mean ‘empirically defensible’
  - E.g. NICE’s estimate does not take account of (positive) qualitative evidence, such as expert opinion

  …otherwise, just hope for a ‘nice surprise’….
- Why might it be worse?
  - If the medicine performs less well in maturing patients, or in real world

Strategic perspectives (manufacturer)

- Probability of further ‘twist’ evidence being beneficial
- Discount required to successfully ‘stick’

Other considerations:

- Cost and feasibility of further evidence generation
- Commercial implications of immediate discount (permanent or temporary) in UK
- Prospect of future reimbursement review

How can we make better-informed decisions?

- Use of additional evidence to predict OS
- Can expert opinion transform hope of a nice surprise, into a realistic expectation?

NEGOTIATING PRICE AND DATA IN AN ERA OF CONDITIONAL APPROVAL: “STICK” OR “TWIST”?

The Role of Expected Value of Information

The University Of Sheffield.

Alan Brennan on behalf of Mark Strong

ScHARR, University of Sheffield, UK

Outline

1. Expected Value of Information as a Payer Thought Experiment - IMAGINE IF …

2. Payer Risk Analysis - work of the NICE Decision Support Unit on Managed Entry Agreements

3. Expected Value of More Evidence to Commercial Sector

Outline

1. Expected Value of Information as a Payer Thought Experiment - IMAGINE IF …

Basics of Cost-effectiveness & Uncertainty

- Costs, QALYs, $\mathrm{ICER} = \frac{\mathrm{CostA} - \mathrm{CostB}}{\mathrm{QALYsA} - \mathrm{QALYsB}}$
- Decision Threshold λ (meaning opportunity cost / willingness to pay)
- Net Monetary Benefit A = λ∗QALYsA − CostA
- $\mathrm{Net\ Health\ Benefit} = \mathrm{QALYsA} - \frac{\mathrm{CostA}}{\lambda}$
- PSA – statistical distributions for all uncertain
- Decision rule: choose strategy with maximum ***expected*** net monetary benefit
- Visualised uncertainty: C-E plane or CEAC, or incremental NB distribution

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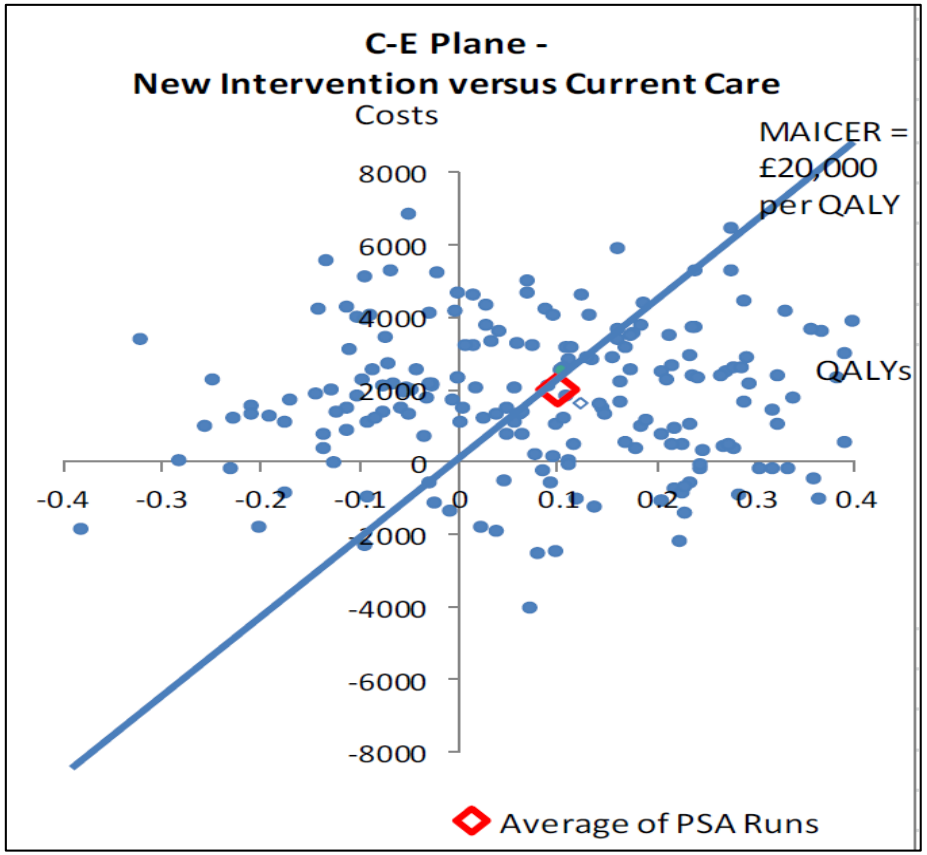


Basic Expected Value of Perfect Information
Payer does a thought experiment ….

- IMAGINE IF … we knew for certain the true value of all uncertain parameters in the health economic model

- THEN …. we would use knowledge to approve only true best strategy

EVPI is the extra net monetary benefit we would ***expect*** to get by revising our decision

MA.ICER	£20,000					
	Net Benefit = QALYs * MA.ICER - Cost			Probability Intervention is most cost-effective	Gain in net monetary benefit if	
PSA Run	New Treatment	Current Care	Difference in Net Monetary Benefit	New Treatment most cost-effective?	all uncertainty were eliminated and decision maker could switch to true optimal	Gain in Net health benefit
1	£160,000	£155,000	£5,000	Yes	£0	-
2	£160,000	£155,000	£5,000	Yes	£0	-
3	£158,000	£155,000	£3,000	Yes	£0	-
4	£156,000	£155,000	£1,000	Yes	£0	-
5	£156,000	£155,000	£1,000	Yes	£0	-
6	£156,000	£155,000	£1,000	Yes	£0	-
7	£156,000	£155,000	£1,000	Yes	£0	-
8	£154,000	£155,000	-£1,000	No	£1,000	0.050
9	£152,000	£155,000	-£3,000	No	£3,000	0.150
10	£152,000	£155,000	-£3,000	No	£3,000	0.150
Average	£156,000	£155,000	£1,000	70%	£700	0.035
	Highest expected net monetary benefit	Expected to be Suboptimal		More likely to be cost-effective	Expected (average) gain in monetary net benefit if all uncertainty were eliminated	

What we ***expect*** to gain if resolve uncertainty?

If truth is like PSA …

Row 1 we would not change decision

Row 2 we would not change decision

…

Row 8 we would change decision & gain £1000

Averaging across all PSA ***expect*** to gain …. £700

This is the EVPI .

Further Expected Value of Information Payer Thought experiments

EVPPI – expected value of perfect parameter information

- IMAGINE IF … we knew for certain the true value of one (or a subgroup of) uncertain parameter

EVSI – sample information

- IMAGINE IF … we obtained more data on the value of some uncertain parameter

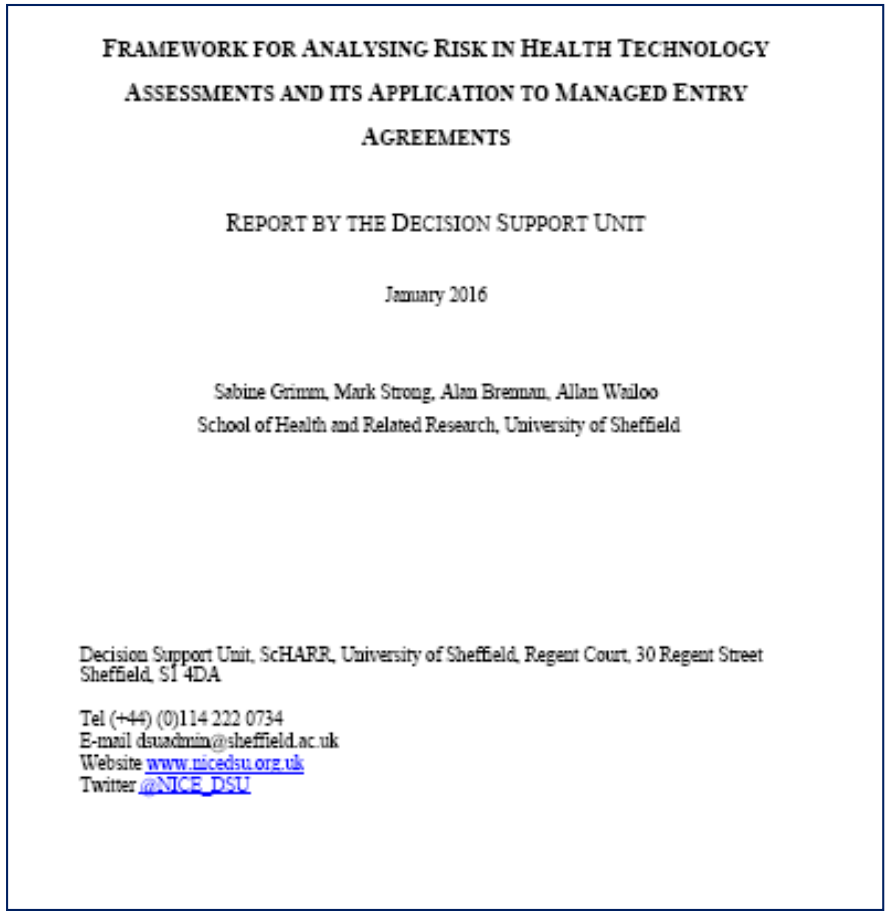
- THEN …. we have lower uncertainty and we would use extra data to update estimates of costs and QALYs and so update our decision

Outline

2. Payer Risk Analysis - work of the NICE Decision Support Unit on Managed Entry Agreements

Payer Risk Analysis

Report to NICE



FRAMEWORK FOR ANALYSING RISK IN HEALTH TECHNOLOGY ASSESSMENTS AND ITS APPLICATION TO MANAGED ENTRY AGREEMENTS

REPORT BY THE DECISION SUPPORT UNIT

January 2016

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ORIGINAL RESEARCH ARTICLE

The HTA Risk Analysis Chart: Visualising the Need for and Potential Value of Managed Entry Agreements in Health Technology Assessment

Sabine Elisabeth Grimm[1] · Mark Strong[2] · Alan Brennan[2] · Allan J. Wailoo[2]

Abstract
Background Recent changes to the regulatory landscape of pharmaceuticals may sometimes require reimbursement authorities to issue guidance on technologies that have a less mature evidence base. Decision makers need to be aware of risks associated with such health technology assessment (HTA) decisions and the potential to manage this risk through managed entry agreements (MEAs).
Objective This work develops methods for quantifying risk associated with specific MEAs and for clearly communicating this to decision makers.
Methods We develop the 'HTA risk analysis chart', in which we present the payer strategy and uncertainty burden (P-SUB) as a measure of overall risk. The P-SUB consists of the payer uncertainty burden (PUB), the risk stemming from decision uncertainty as to which is the truly optimal technology from the relevant set of technologies, and the payer strategy burden (PSB), the additional risk of approving a technology that is not expected to be optimal. We demonstrate the approach using three recent technology appraisals from the UK National Institute for Health and Clinical Excellence (NICE), each of which considered a price-based MEA.
Results The HTA risk analysis chart was calculated using results from standard probabilistic sensitivity analyses. In all three HTAs, the new interventions were associated with substantial risk as measured by the P-SUB. For one of these technologies, the P-SUB was reduced to zero with the proposed price reduction, making this intervention cost effective with near complete certainty. For the other two, the risk reduced substantially with a much reduced PSB and a slightly increased PUB.
Conclusions The HTA risk analysis chart shows the risk that the healthcare payer incurs under unresolved decision uncertainty and when considering recommending a technology that is not expected to be optimal given current evidence. This allows the simultaneous consideration of financial and data-collection MEA schemes in an easily understood format. The use of HTA risk analysis charts will help to ensure that MEAs are considered within a standard utility-maximising health economic decision-making framework.

Key Points for the Decision Maker

The health technology assessment (HTA) risk analysis chart presents a standardised visualisation to show the need for and potential value of different classes of managed entry agreement (MEA) schemes.

Its use in HTA could ensure that MEAs are considered routinely, consistently and transparently.

The HTA risk analysis chart allows for simultaneous consideration of financial and data-collection MEA schemes.

1 Introduction

Recent changes to the regulatory landscape of pharmaceuticals, such as adaptive pathways or conditional licensing schemes [1, 2] issued by the European Medicines

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http://scharr.dept.shef.ac.uk/nicedsu/methods-development/managed-entry-agreements-mea/

Risk Analysis: Hypothetical example (All we need are PSA results)

	Intervention 1	Intervention 2	Intervention 3
Expected QALYs	8.0	8.1	8.2
Expected Costs	£6,000	£7,000	£8,000
ICER (v Int 2)			**£10,000 /QALY**
Net £ Benefit (£20k)	£154,000	£155,000	£156,000
Expected Net Health Benefit (QALYs)	7.7	7.75	7. 8

PSA results:

- Intervention 3 has 70% probability of being most cost-effective
- PUB (=EVPI) per patient on monetary scale is £700
- PUB (=EVPI) per patient on QALY scale is 0.035 QALYs worth of uncertainty

Risk Analysis: Hypothetical example (All we need are PSA results)

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Net £ Benefit (£20k)	£154,000	£155,000	£156,000
Expected Net Health Benefit (QALYs)	7.7	7.75	7. 8
PUB (=EVPI) (QALYs)	0.035	0.035	0.035
PSB (QALYs)	0.1	0.05	0
P-SUB (PUB+PSB)	0.135	0.085	0.035

For the England population (10,000 people affected) this means…

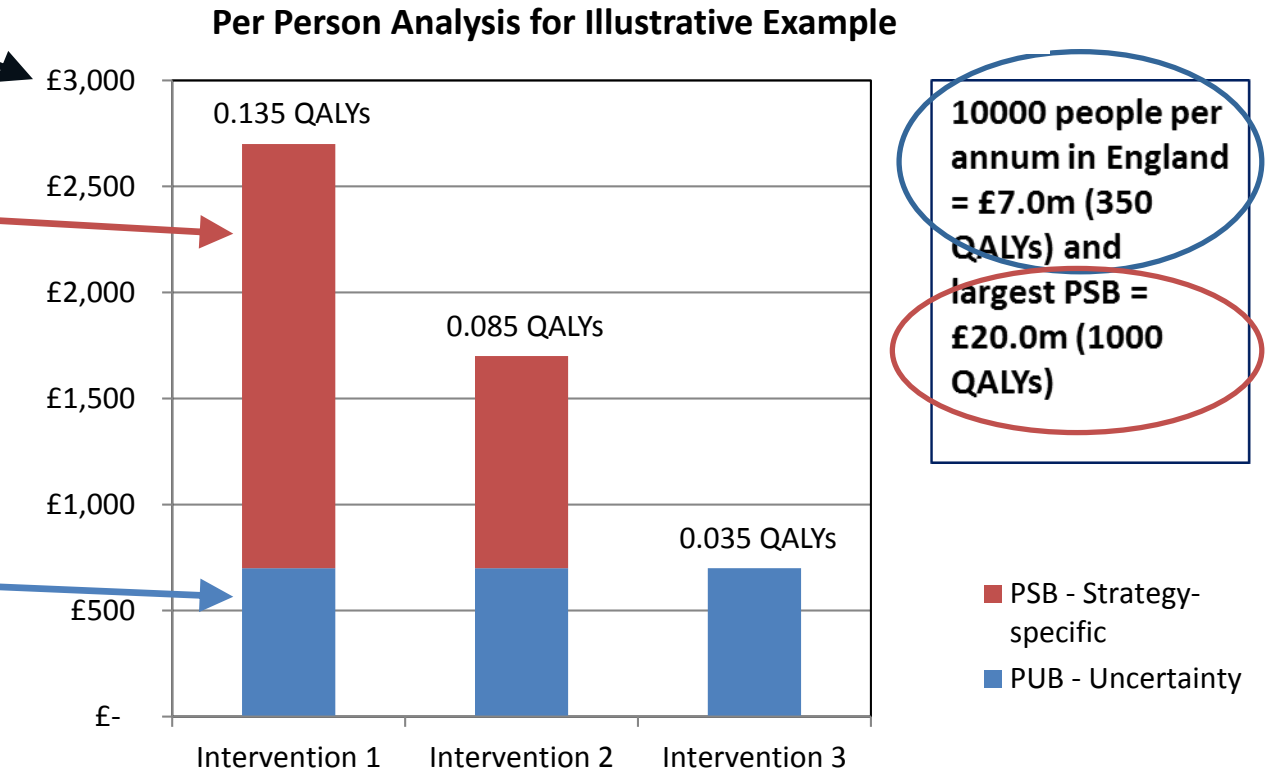
PUB (=EVPI) (QALYs)	350	350	350
PSB (QALYs)	1000	500	0
P-SUB (QALYs)	1350	850	350

Risk Analysis Chart:- Hypothetical example

Note scale on Y axis is £3,000 (0.15 QALYs)

A lot of red implies that a price reduction is needed

A lot of blue implies that research is needed – but price reductions could also reduce the PUB



10000 people per annum in England = £7.0m (350 QALYs) and largest PSB = £20.0m (1000 QALYs)

So for Intervention 1
NICE might like to see
- **reduction in price**
- **Extra evidence to reduce uncertainty**

A change in price or evidence can:
- **Change the size of the bars**
- **Change the mix of blue and red**

A real world example
We assessed 5 MEA options for Pazopinib NICE appraisal

No.	MEA	Details
1	Discount	Discount already proposed by manufacturer
2	COMPARZ trial	COMPARZ trial of Pazopanib v Sunitinib already ongoing (Conditional licensing) Re-Appraisal would re-assess cost-effectiveness
3	Discount & COMPARZ trial	Combine 1 & 2
4	Money back guarantee scheme (Scheme A)	Money back if patient's survival time is shorter than the expected survival time that could have been achieved with interferon-alpha
5	Scheme A & monitoring registry data for 2 years, then re-appraisal	Exactly the same scheme as above Plus monitoring registry data that can reduce uncertainty in the future monitoring registry data for 2 years, then re-appraisal

Risk Analysis: Pazopanib for renal cell carcinoma (TA215, 2011)

PSA results (50,000 PSA runs)	Pazopanib	Sunitinib	Interferon-α	Best supportive care
Expected QALYs	2.02	1.90	1.25	0.99
Expected Costs (£)	£ 40,148	£ 36,366	£ 8,383	£ 4,103
ICER against interferon-α	£ 41,100	£ 42,767		
ICER against sunitinib	**£ 31,901 per QALY**	-		
Expected net monetary benefit (MA.ICER=£20k/QALY)	£ 284	£ 1,695	£ 16,591	£ 15,708
Expected net monetary benefit (EoL: MA.ICERs related to incremental survival gain)	£ 25,007 Rank=1st	£ 22,925	£ 16,591	£ 15,708

Pazopanib expected to be most effective, but most costly

Pazopanib is largest expected net benefit

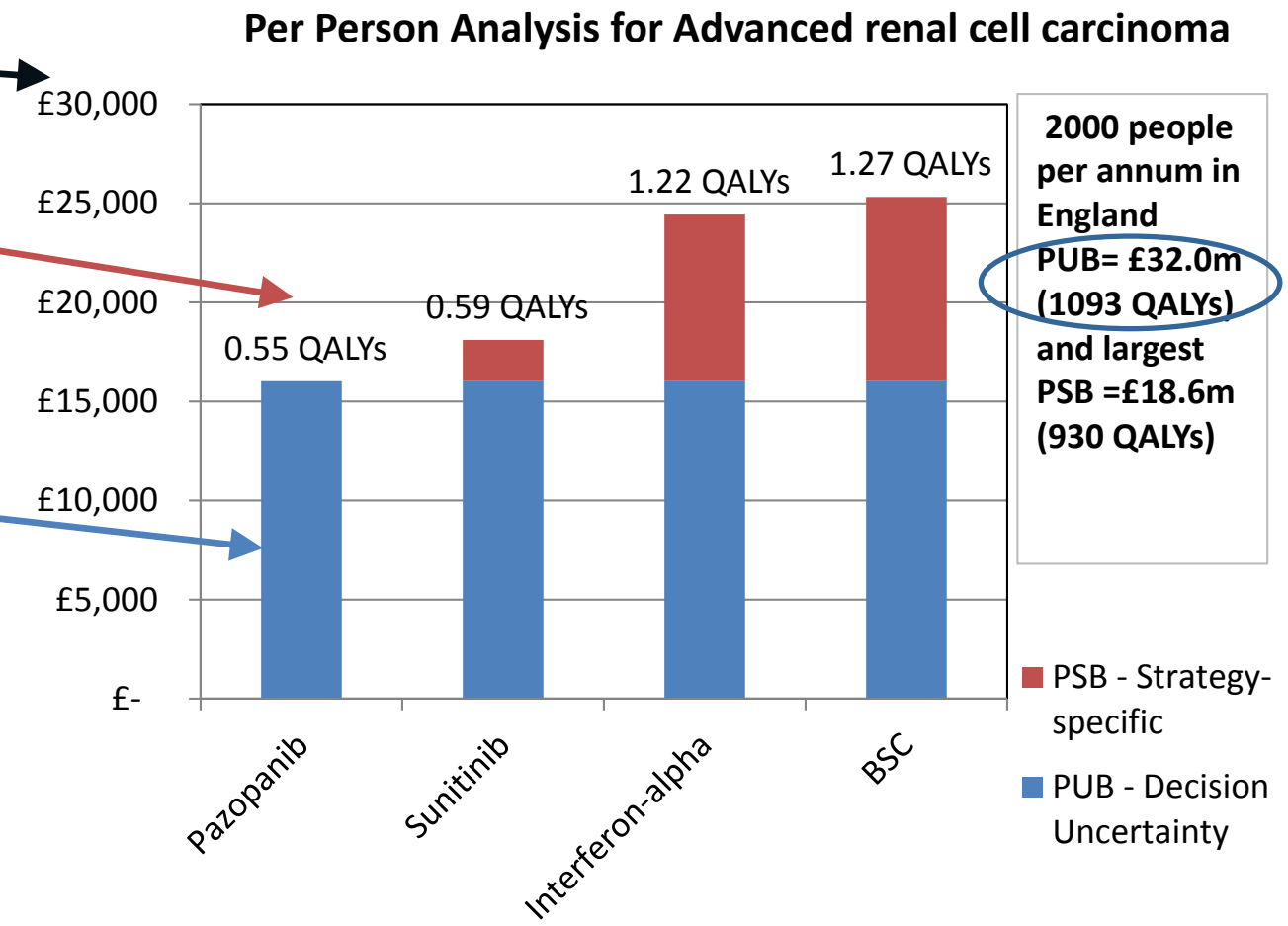
Pazopanib marketing authorisation was conditional on head-to-head non-inferiority trial of pazopanib versus sunitinib (COMPARZ).

Risk Analysis Chart: Pazopanib given current evidence & prices (EoL valuation - variable MA.ICER)

Note scale on Y axis is £30,000 10 times higher than our earlier hypothetical example

Pazopanib has no strategy-risk burden

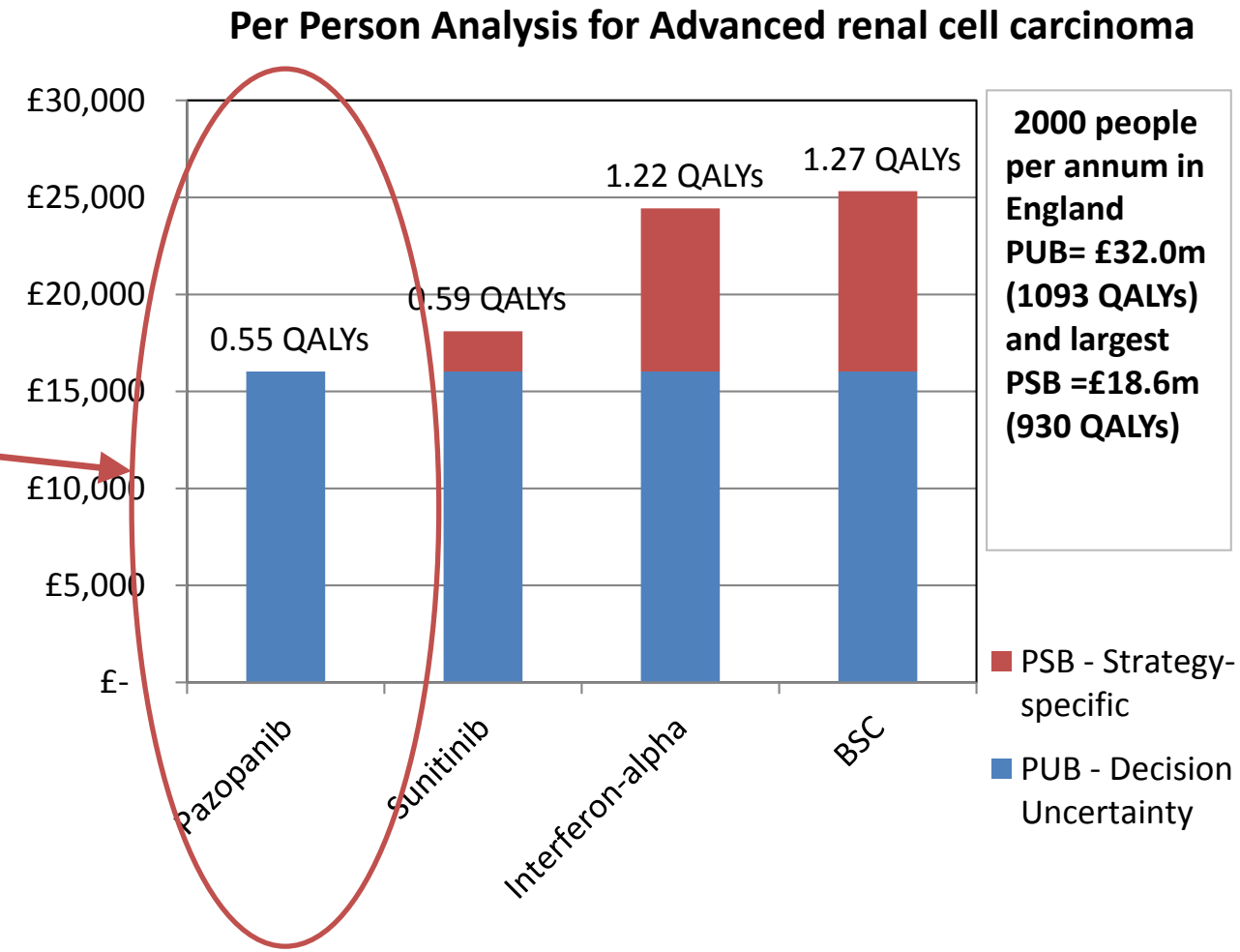
But there is a huge uncertainty burden: Implies need for additional evidence



We assessed 5 MEA options for the Pazopinib appraisal

We now look at the pazopanib bar only …

…And see how MEA schemes reduce it



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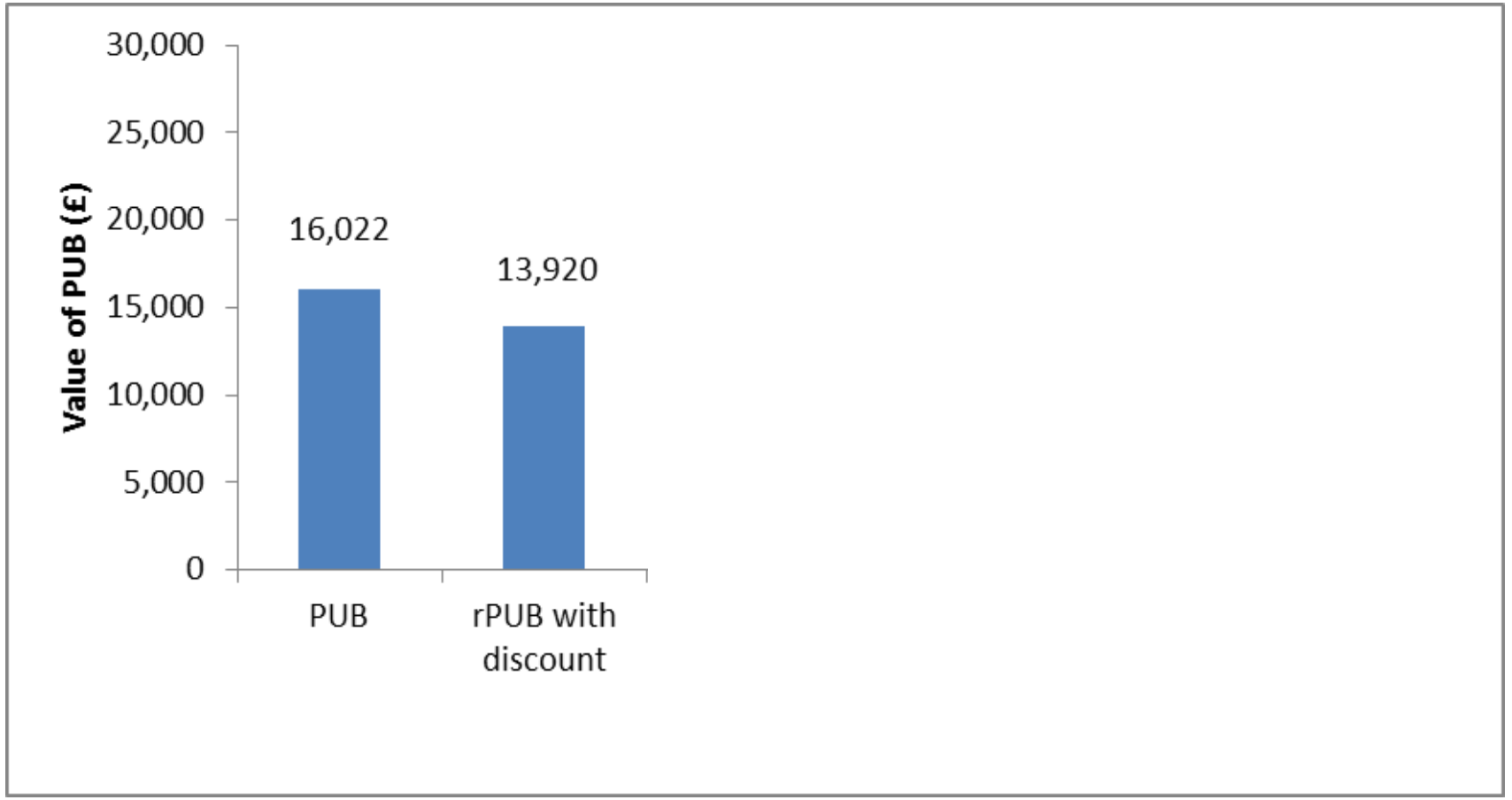

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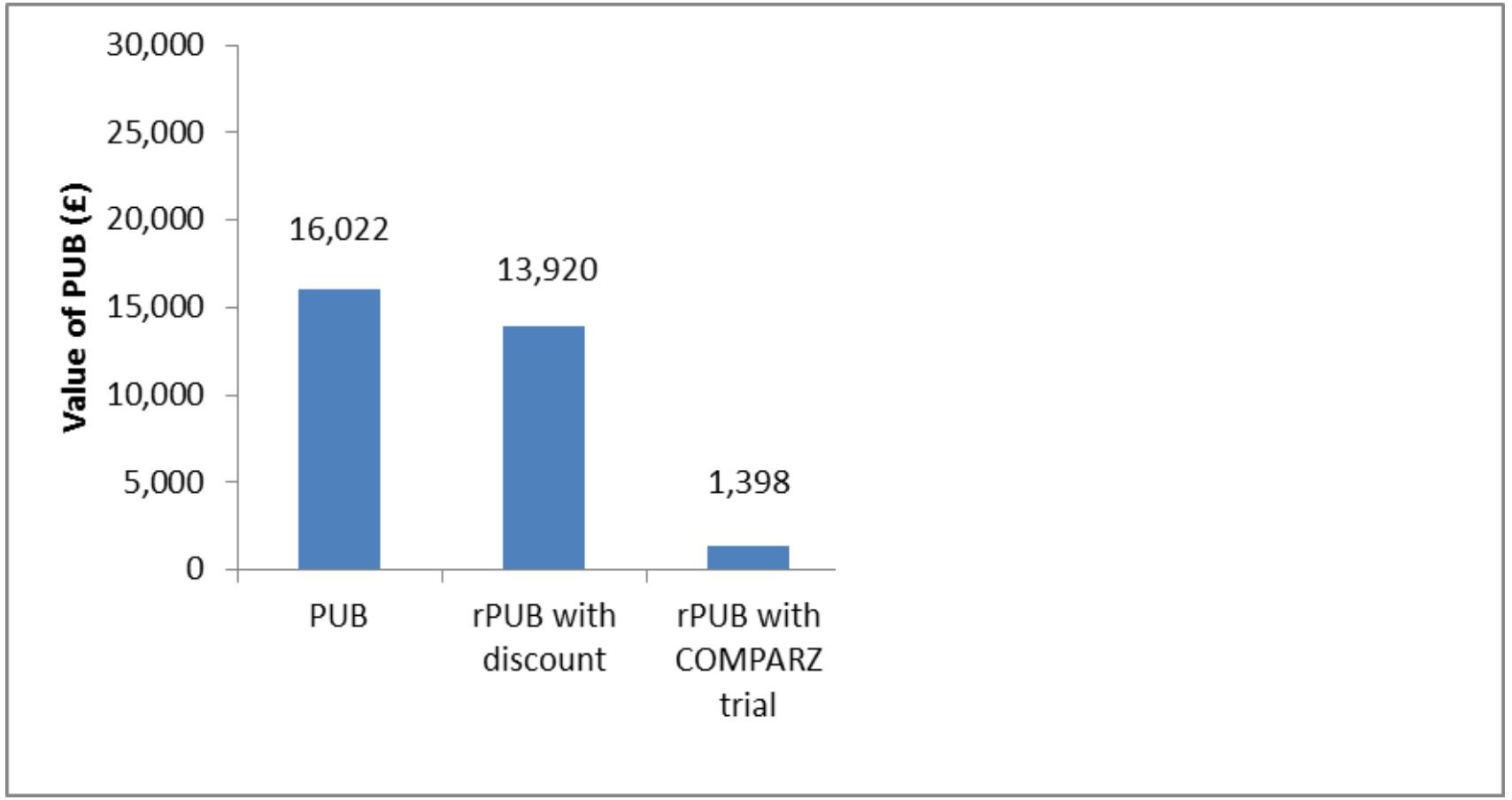

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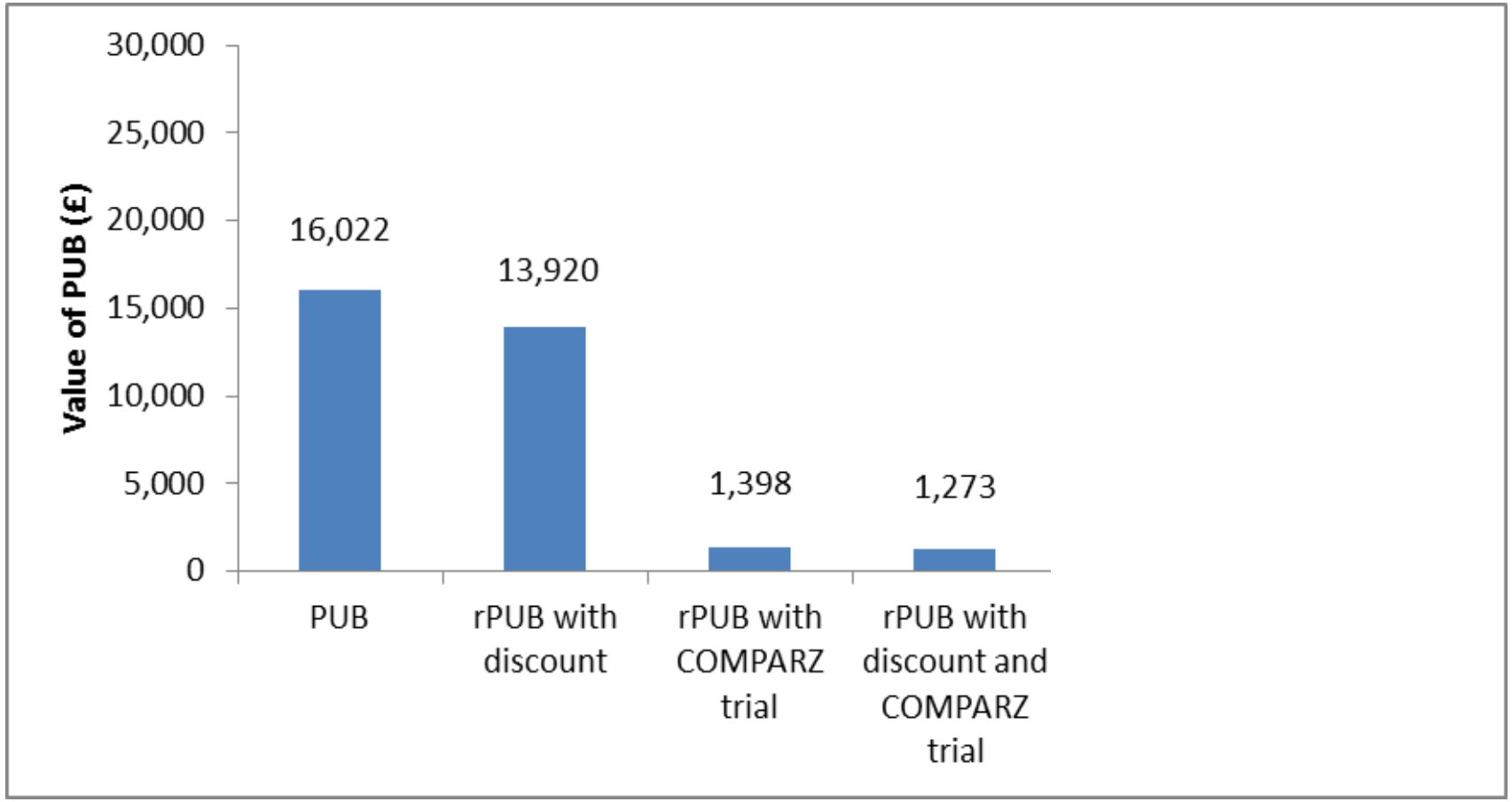

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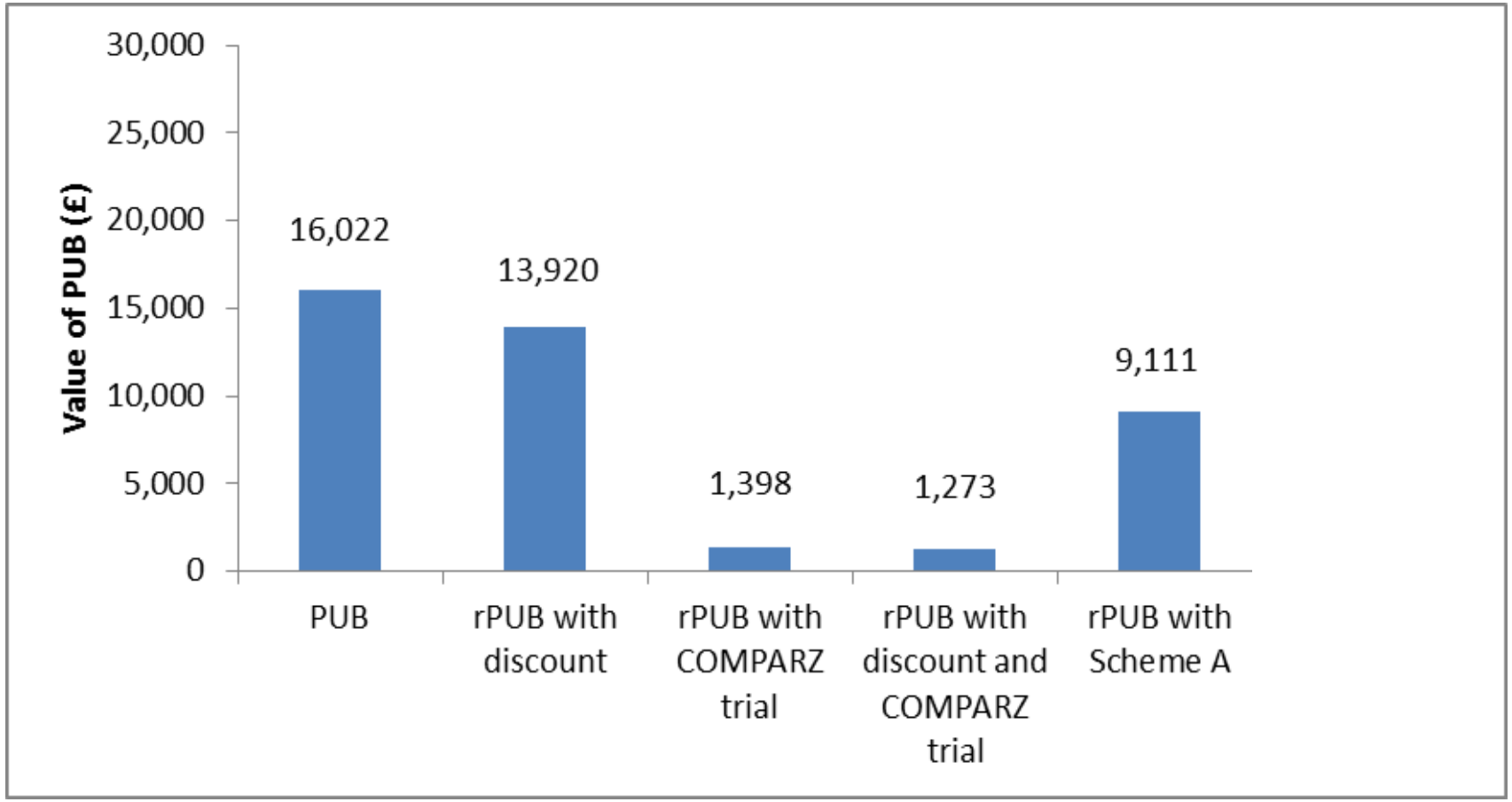

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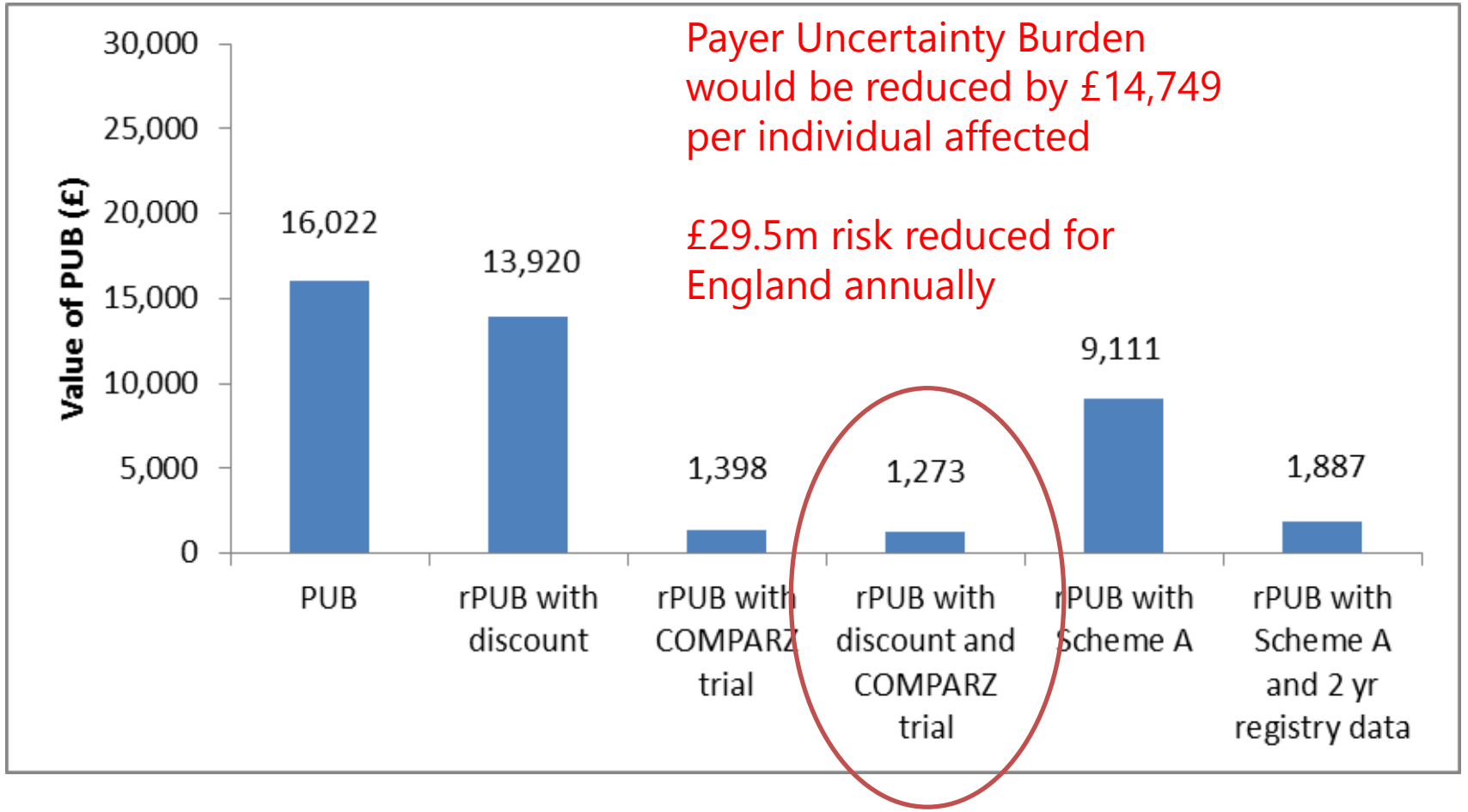

Implications of Payer Risk Analysis for the “Stick or Twist Decision” a Company has to make

Company can use Risk Analysis Chart …

- before NICE appraisal submission to understand how NICE might examine risks given current evidence
- after NICE ACD to understand how NICE might quantify risks given “most plausible model”
- before proposing an MEA to consider options for proposed MEAs (both price & evidence) and work out how much each option would reduce Payer Risk Burden

Outline

3. Expected Value of More Evidence to Commercial Sector

HEALTH ECONOMICS
Health Econ. **24**: 1468–1482 (2015)
Published online 9 September 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/hec.3103

VALUING TRIAL DESIGNS FROM A PHARMACEUTICAL PERSPECTIVE USING VALUE-BASED PRICING

PENNY BREEZE*,* and ALAN BRENNAN

School of Health and Related Research, University of Sheffield, Sheffield, UK

Breeze & Brennan Abstract

- Adapt traditional framework for expected net benefit to be compatible with drug development trials from the pharmaceutical perspective.
- Assume price of drug is set conditional on trial outcomes to achieve NICE threshold for being cost-effective
- Assume there is a threshold price below which the company would not market the new intervention.
- Case study phase III trial - sample size and trial duration are varied.
- For each design, sample 10,000 trial outcomes and estimate 10,000 prices
- Expected commercial net benefit = expected profits minus trial costs
- Results
- Trial with short follow-up but large sample size gave greatest expected commercial net benefit.
- Increasing duration of follow-up had a modest impact.

NEGOTIATING PRICE AND DATA IN AN ERA OF CONDITIONAL APPROVAL: “STICK” OR “TWIST”?

Thank You

The Role of Expected Value of Information

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ScHARR, University of Sheffield, UK

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Your Success.

W22: Negotiating price and data in an era of conditional approval: “Stick” or “Twist”?

Ash Bullement
Health Economist
Wednesday 8 November, 2017
ISPOR 20th Annual European Congress

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Topic of discussion

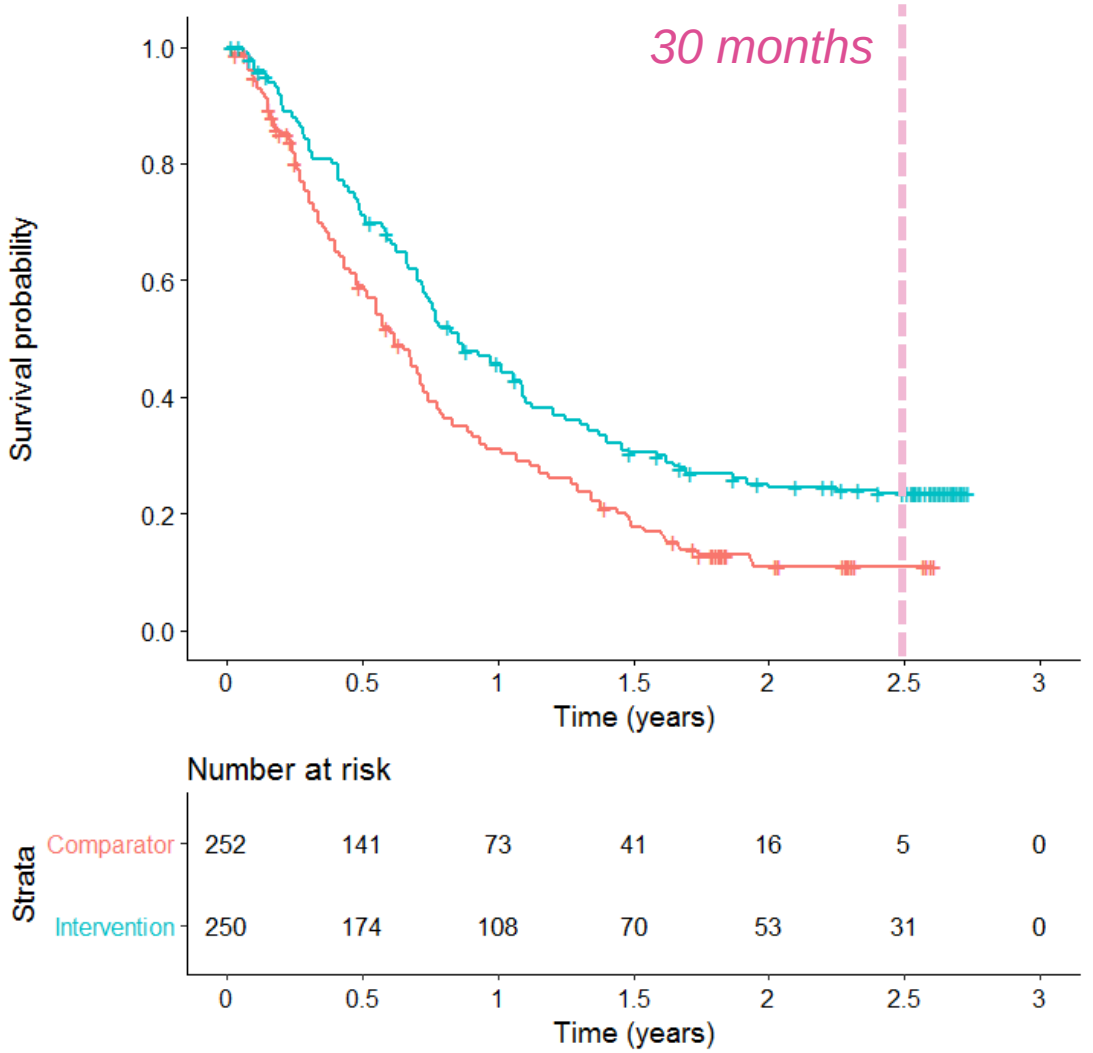
- Using a hypothetical case study, illustrate how simulation methods can be used to estimate the expected commercial value of information derived from a trial extension
  - Hypothetical case study: data for an example disease to illustrate methodology
  - Simulation methods: sampling methodology to estimate future outcomes
  - Expected commercial value of information (ECVI) i.e. the value at which a product can be justifiably priced, based on available evidence
  - Trial extension: further follow-up data collected while interim funding is made available

Background

- Recent advancements in cancer immunotherapy have demonstrated promising results
  - Trade-offs between robust (long-term) survival estimates and timely access to new treatments
- Conditional approval gives manufacturers an opportunity to provide interim access to new treatments while collecting further data
  - However, the price charged in this interim period should be considered allowable (or economically justifiable) with current (incomplete) empirical evidence and clinical expectation
- This analysis aims to illustrate how an economically-justifiable price (EJP) obtained through trial extension may be estimated

Data: Case study

- A hypothetical case study was used to inform the analysis
  - Kaplan-Meier data were produced, demonstrating the common themes expected in immunotherapy survival data, namely:
    - Initial high risk of mortality
    - Lower risk of mortality after this period
    - Early signs of *"survival plateau"*
    - A sizeable number of patients still at risk of an event by the end of trial follow up



Methods

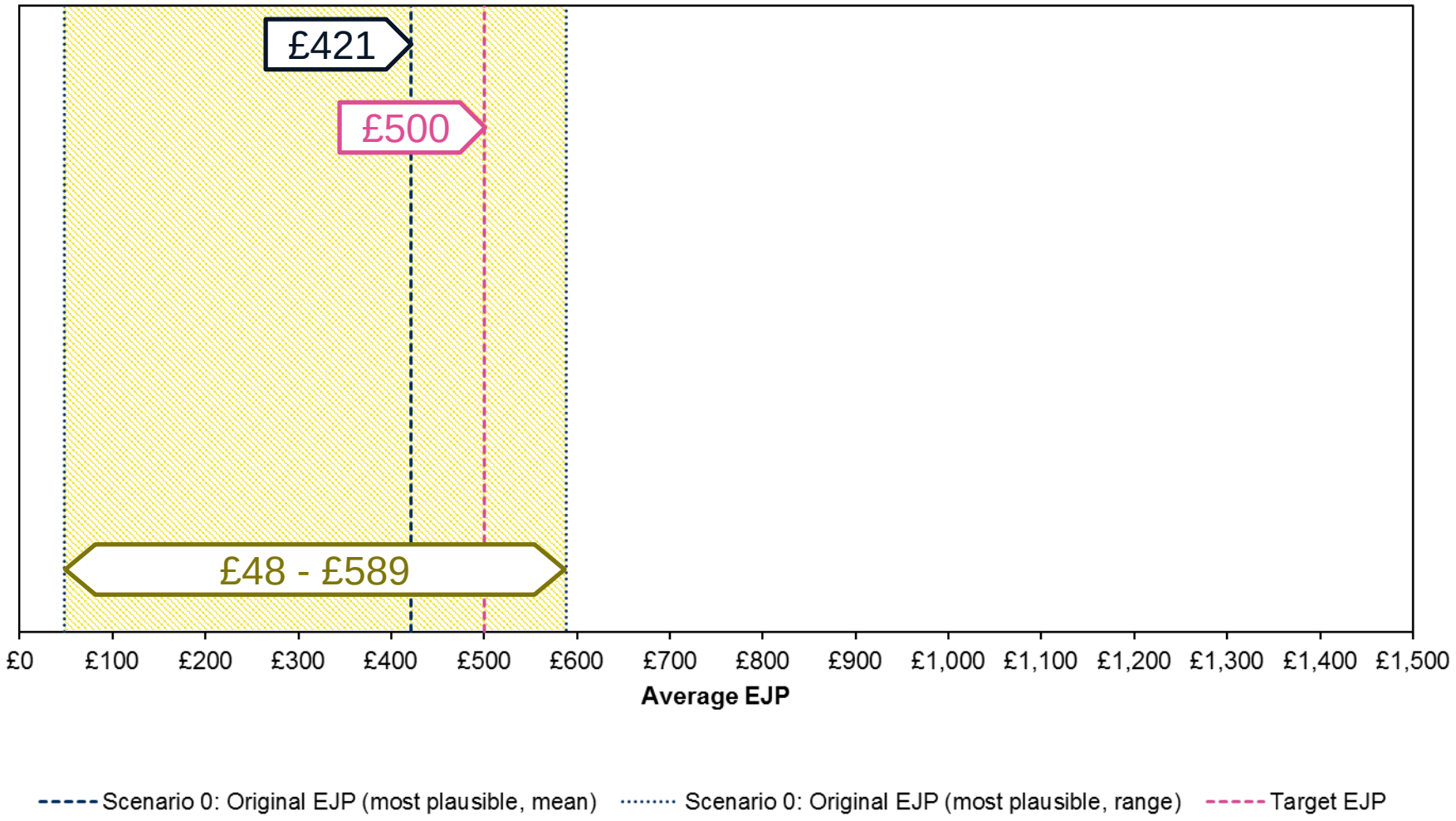
- At risk patients had their survival times predicted over the anticipated follow-up period (30 months), using the statistical package *R*
  - Survival was based on whether they were assumed to be *“cured”* or *“uncured”*
- A Weibull mixture-cure model was used in our analysis, and was implemented into a *“back of the envelope”* cost-effectiveness Excel model to produce ICER estimates
- Using repeated sampling estimates from *R* combined with standard probabilistic sensitivity analysis methods, it was possible to obtain the EJP for each simulation
  - The mean EJP was then calculated, and inferences around its distribution made

Results

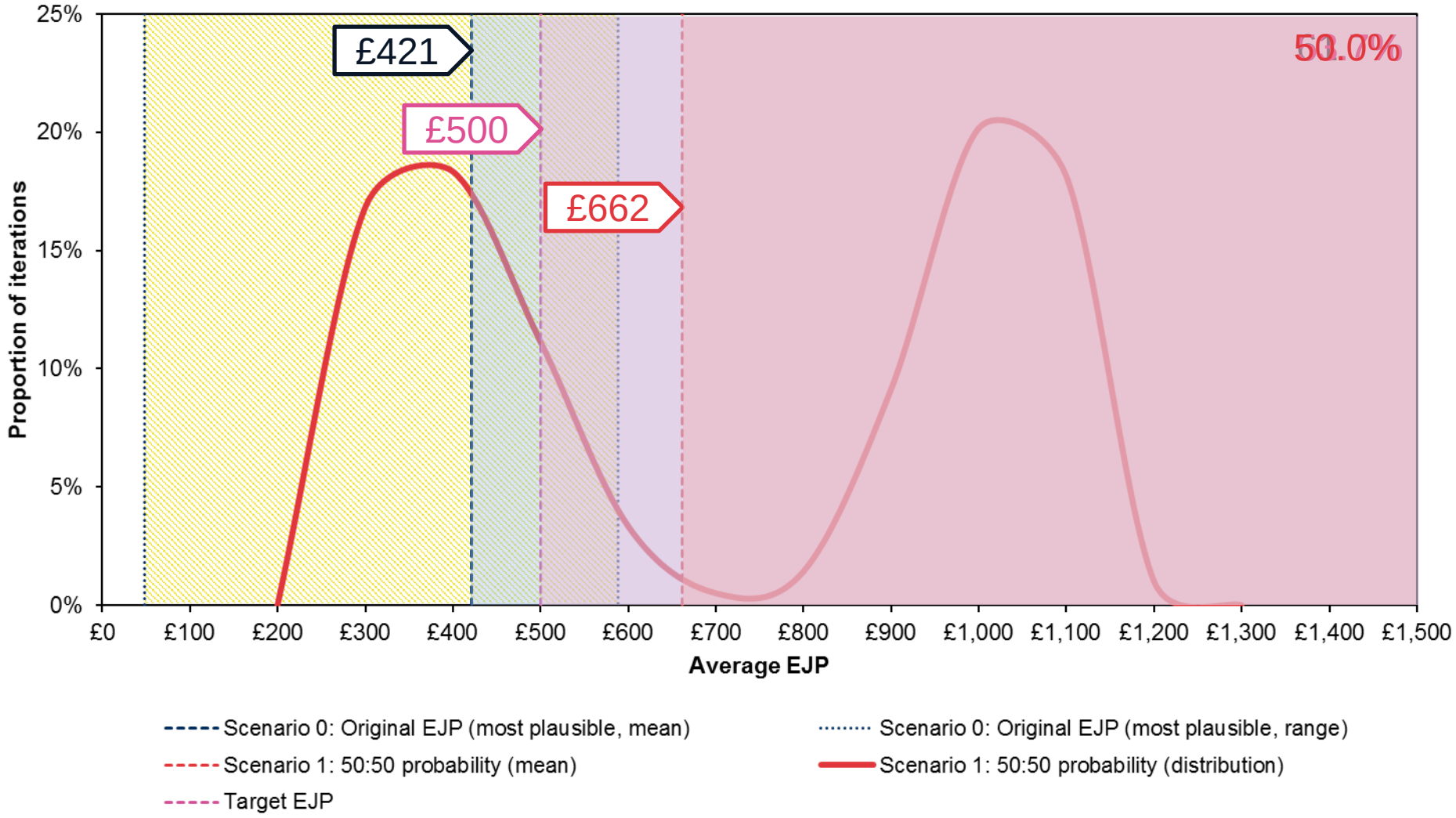
- The outputs produced from this analysis may be summarised as:
  - What is the expected price without simulation? (i.e. *"current" or "Stick"* price)
  - What is the expected price with simulation? (i.e. *"estimated"* or *"Twist"* price)
  - What is the probability of obtaining a price higher than *"current"* price?
  - What is the probability of obtaining a price high enough to be "*worthwhile*"?

    (i.e. above or below what may be considered a "target" price)
- To illustrate this in a variety of situations, two examples have been considered:
  - Scenario 1: 50:50 probability of long-term survivors
  - Scenario 2: 75:25 probability of long-term survivors

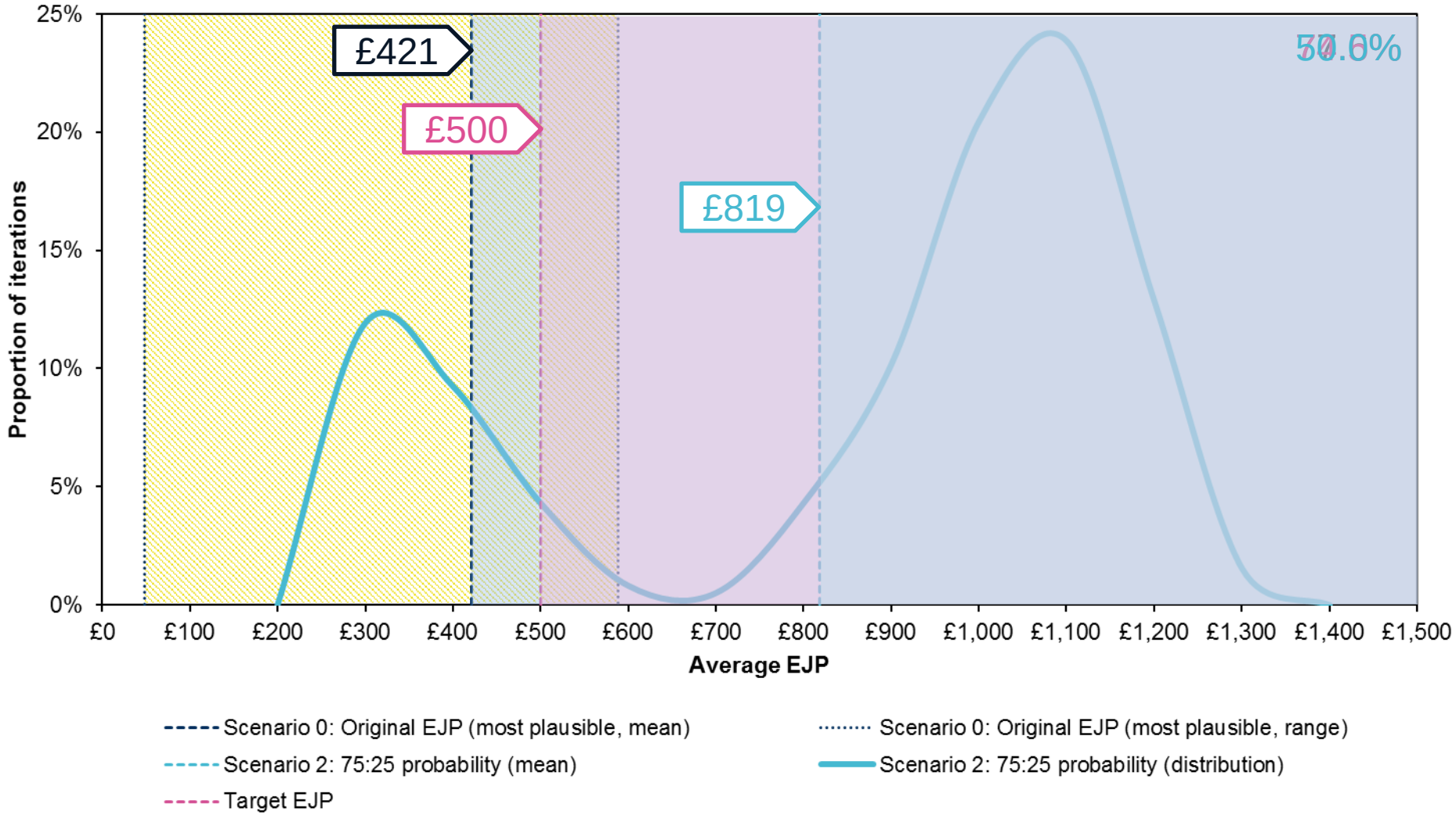
Scenario 0: Original EJP (based on current data)



Scenario 1: 50:50 probability of long-term survivors



Scenario 2: 75:25 probability of long-term survivors



Conclusions

- Simulation methods present a valuable framework for pharmaceutical companies to understand the benefits and risks associated with conditional approval
- Expert elicitation methods may be useful to consider in line with simulation methods in order to produce transparent estimates of long-term survival, which may be using for manufacturer decision making
- This case study presents one possible method that may be used, though simulation methods within the context of conditional approval are an emergent area of research

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