Issues with Indirect Comparisons

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Agenda

Agenda Items
Introduction to Health Economics
Methods for making Indirect Comparisons
Issue 1: Data Extraction
Issue 2: Metric
Issue 3: Multiple Endpoints

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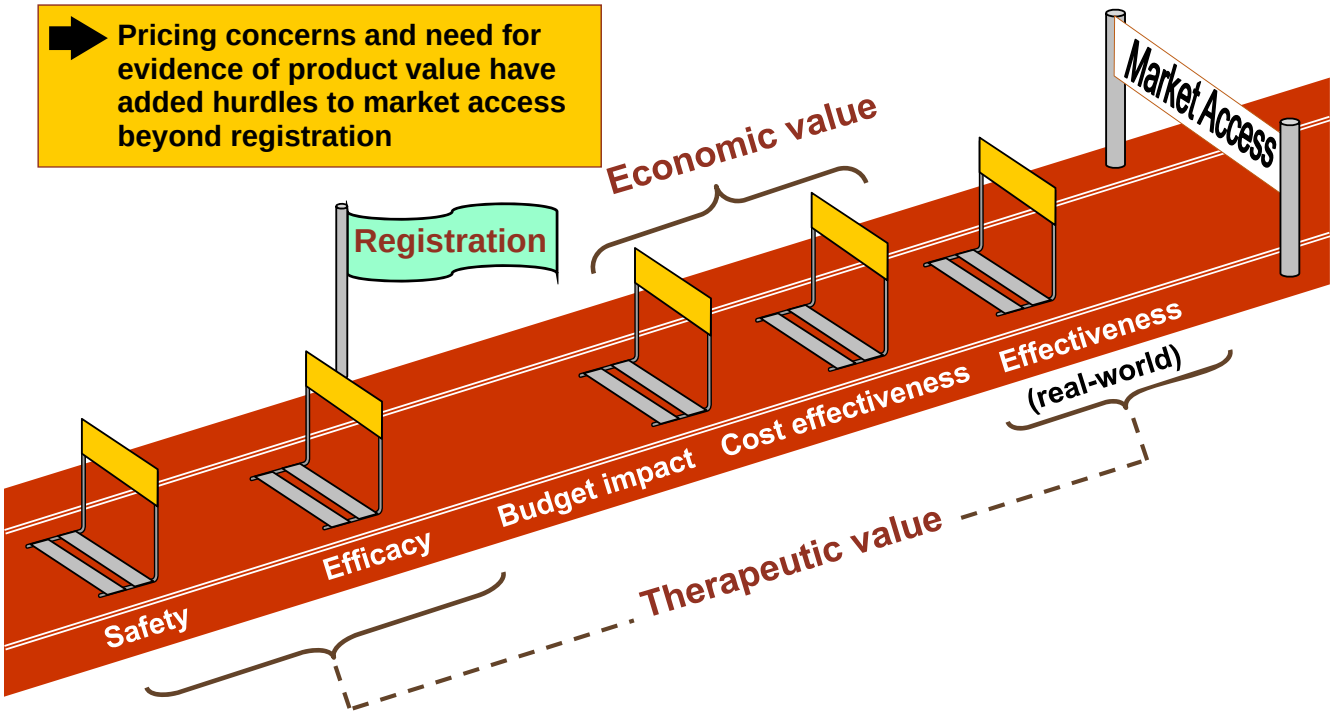
Registration only the first step towards market access

Pricing concerns and need for evidence of product value have added hurdles to market access beyond registration



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What challenges are we facing?

NHS 'preparing to cut millions of operations': Patients will lose out to ensure £20bn savings

Mail Online
Friday, Jun 04 2010

- Primary care trusts, which commission care, are already compiling lists of "low value" operations that would no longer be provided
- These lists are clothed in the language of evidence but they represent target reductions based on cost and volume, sometimes ignoring the potential benefit to individual patients.
- Earlier this year, the Government's rationing body said more cuts in medical treatments are planned to save the NHS at least £600 million.

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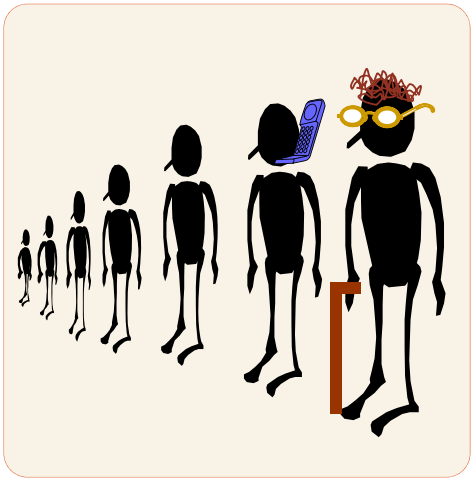
Payer Dilemma: not everything is affordable for all patients

Limited Resources



Infinite + Changing Demand

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Need to show overall value of products

- How do we measure “overall value”?
- How does it relate to development of pharmaceuticals?
- Consider the next couple examples to get a feel for how value is assessed.

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Which one would you choose?

Lipstick A lasts 4 hours **costs € 4**

Lipstick B lasts 24 hours **costs € 24**

Extra 20 hours costs €20, are you willing to pay for this? Is this good overall value? Why or why not?

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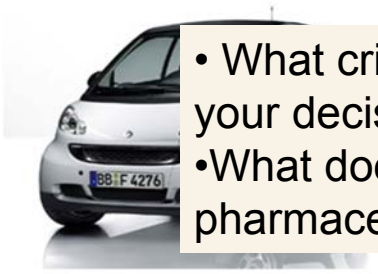
Which one offers better overall value?



• What criteria did you use to make your decision?
•What does this have to do with pharmaceuticals?

- Price: 9,990 EUR
- Passengers: 2
- Space: 220 – 340 L
- Fuel: 4.3 L/100 km (54mpg)
- CO_2 Emissions: 103 g/km
- Airbags: 2
- 0 – 100 km/h in 16.7 sec
- Fun factor: X

- Price: 46,150 EUR
- Passengers: 2
- Space: 280 L
- Fuel: 9.4 L/100 km (25mpg)
- CO_2 Emissions: 221 g/km
- Airbags: 2
- 0 – 100 km/h in 5.9 sec
- Fun factor: >>X

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Reconsider the criteria...

Price: 9,990 EUR	Cost	Price: 46,150 EUR
Passengers: 2	Efficacy	Passengers: 2
Space: 220 – 340 L		
Fuel: 4.3 L/100 km (54mpg)		
CO_2 Emissions: 103 g/km	Safety	CO_2 Emissions: 221 g/km
Airbags: 2		Airbags: 2
0 – 100 km/h in 16.7 sec	QoL	0 – 100 km/h in 5.9 sec
Fun factor: X		Fun factor: >>X

Need to combine these criteria to define overall value

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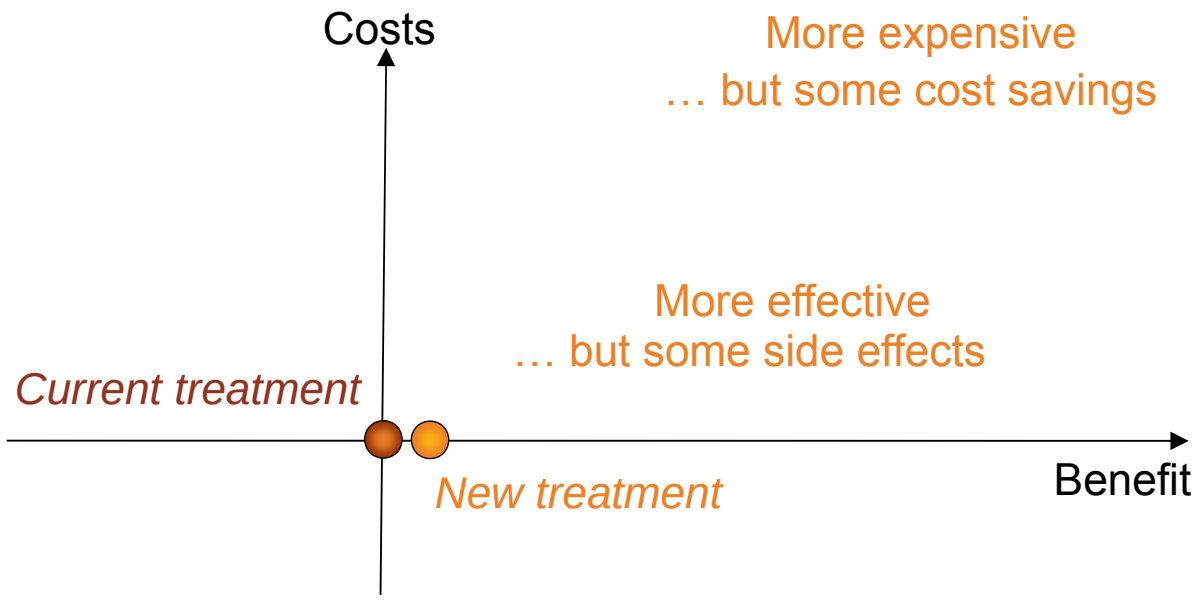
Trading off benefits, harms and costs

How do you get cost/benefit?



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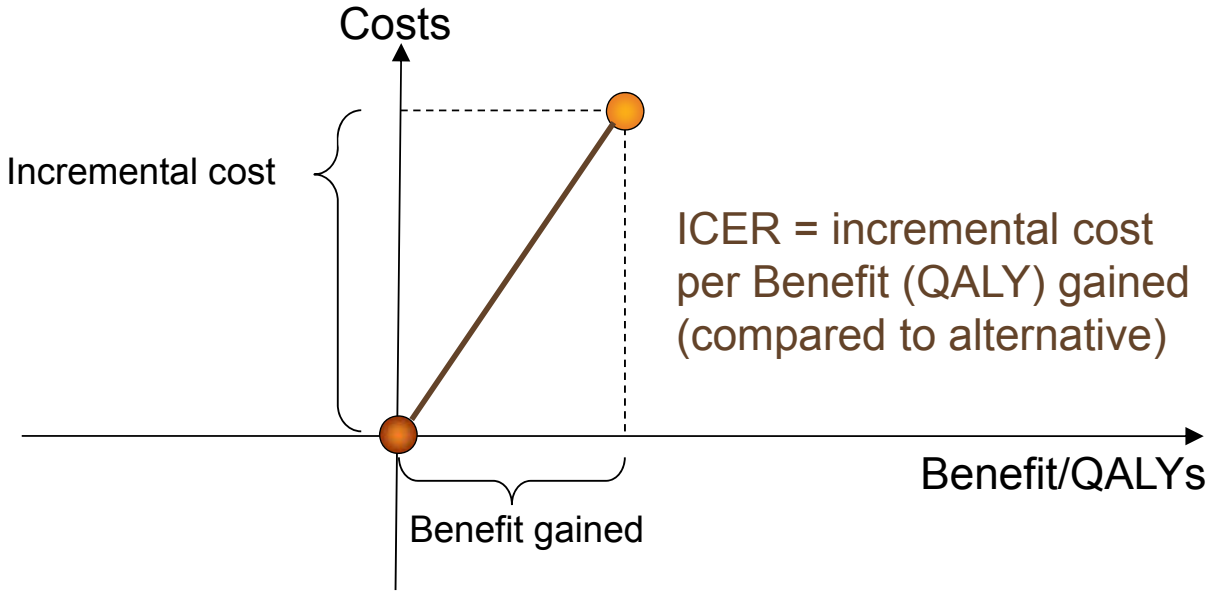
Cost Effectiveness is a technique for quantifying overall value

- If the ICER is within an acceptable range (threshold) defined by the healthcare payer/provider, then the treatment is likely to be accepted



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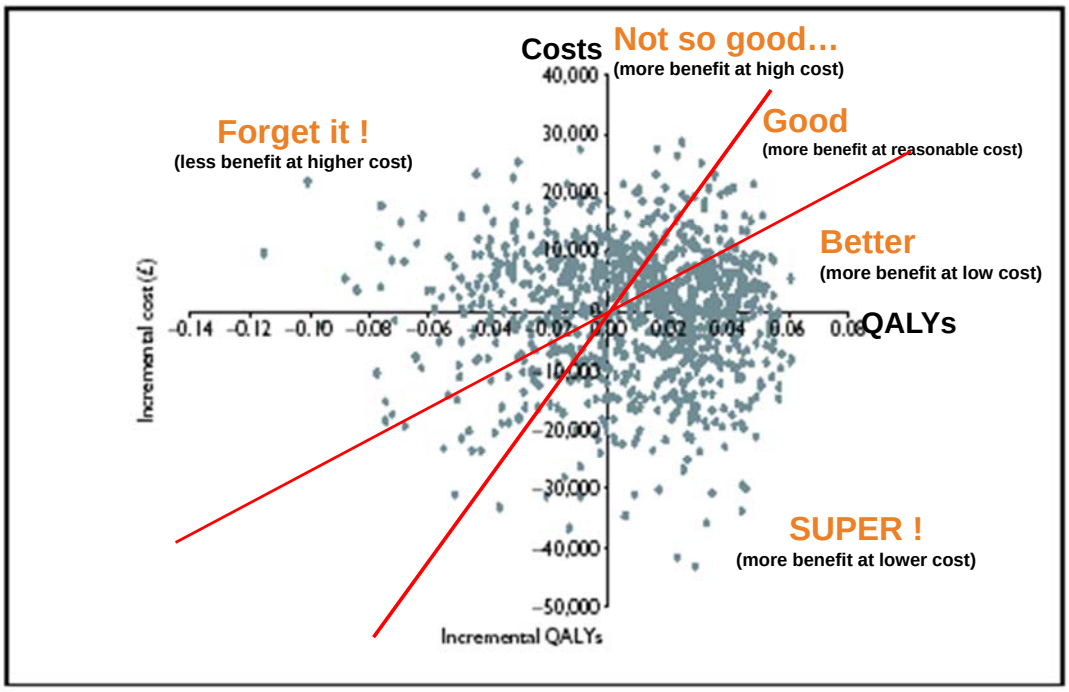
Cost-effectiveness: Tool for decision making

Good overall value?



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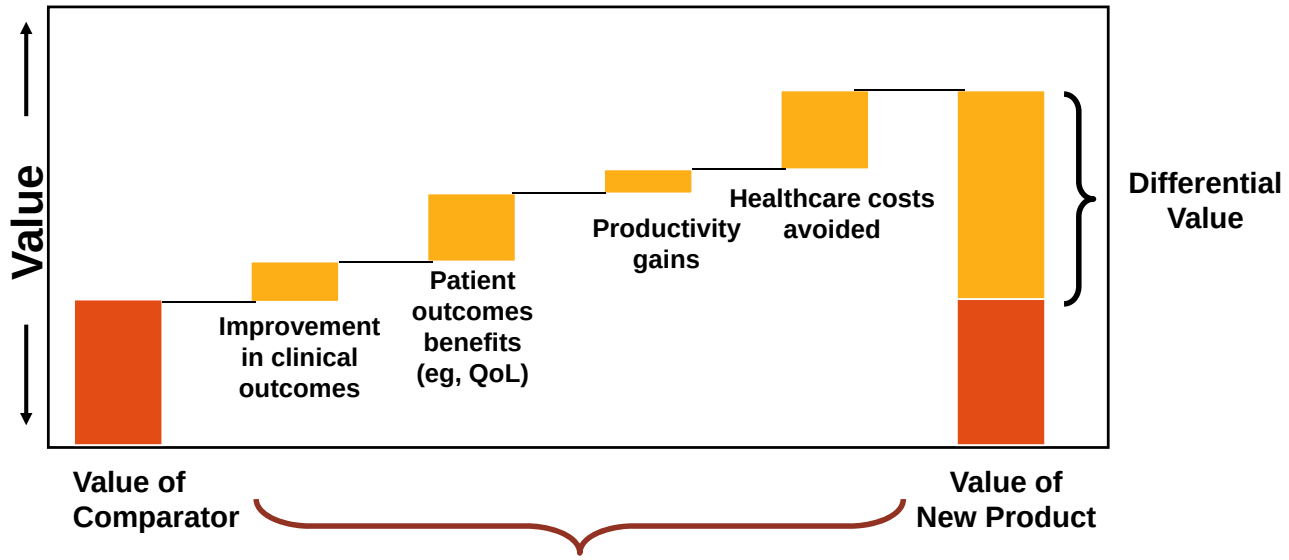
Demonstrating Differential Value of our Products

Ideal Scenario



HE&OR conducts studies and develops models to quantify the differential value our products bring to customers

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Indirect Comparison

- Refers to a comparison of different healthcare interventions using data from separate studies, in contrast to a direct comparison within randomised controlled trials
- Often used because of a lack of, or insufficient, evidence from head-to-head comparative trials

Naive indirect comparison

- Individual arms from different trials compared as if they were from the same randomised trials
- To be avoided in analysing data from randomised trials

Adjusted indirect comparison

- Comparison of treatments adjusted with a common control
- Usually consistent with direct comparison results

Basic assumptions underlying indirect comparisons:

Homogeneity assumption-	Similarity assumption-	Consistency assumption-
for standard meta-analysis	for adjusted indirect comparison	for the combination of direct and indirect evidence

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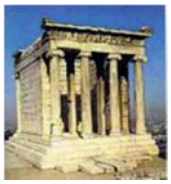
Simple Comparison



Athena Nike

<

Parthenon

Athena Nike smaller than Parthenon

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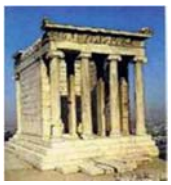
Poseidon at Sounion

Parthenon smaller than Poseidon at Sounion



?

A<B, B<C → A<C
Therefore, Nike smaller than Poseidon

Easy comparison because we can measure directly

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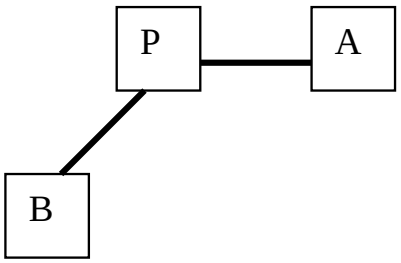
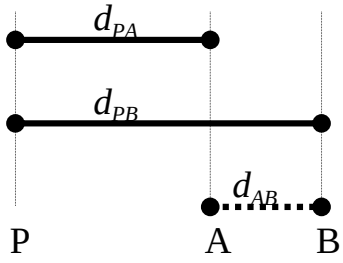
Indirect comparison – simple case





$$d_{AB} = d_{PB} - d_{PA}$$

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Indirect Comparison – Simple Case 1

'Trial 1: Porsche versus Golf'

Porsche - Golf = 2s

'Trial 2: Volvo versus Golf'

Volvo - Golf = 8s

→ **Indirect Comparison:**
Volvo versus Porsche: 8-2=6s

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Volvo faster than a Porsche?

- Do you believe it?
- Why or why not?
- Were the trials equal? Were they done in the same setting?
- Trial 1: Race was in the snow
- Trial 2: Race was on a dry road
- Road conditions might have influenced the results
- Can we adjust for the differences?

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Standard Methods for making Indirect Comparisons

I. Bucher Indirect Treatment Comparison:

II. Lumley Network Meta-analysis for Indirect Treatment Comparisons

III. Models for Multi-parameter Synthesis and Consistency of Evidence

IV. Sampling method for indirect comparison using individual patient data for just one treatment

V. Mixed Treatment Comparison Method

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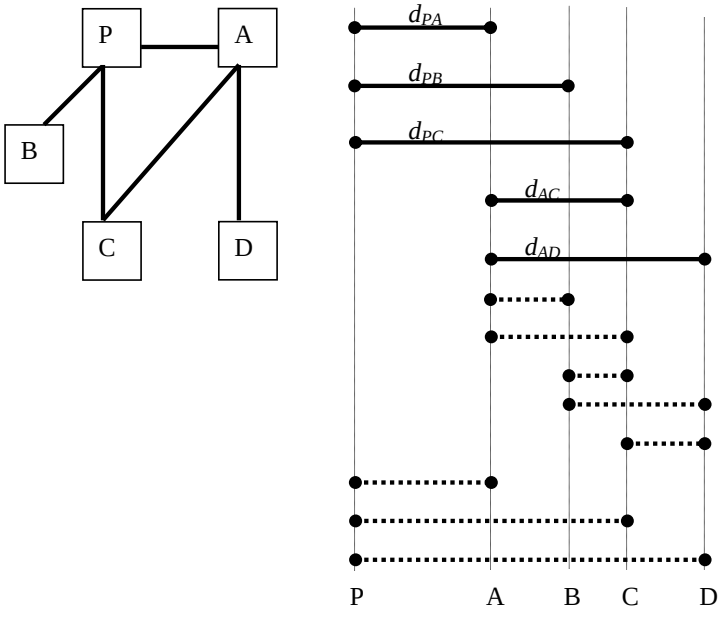
Mixed Treatment Comparisons



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Issue 1: Data Extraction

Example from Osteoporosis

Want to compare the RR on non-vertebral fractures of alendronate to etidronate

- Alendronate: multiple trials comparing alendronate to placebo
- Etidronate: the same

One approach is the Bucher approach, i.e. meta-analysis for each compound against placebo and a “comparison” of the meta-analysis results

- Canadian reimbursement agency: alendronate 5 studies
- UK NICE: alendronate 6 studies
- Cochrane analysis: alendronate 6 studies

But, it gets worse...

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Do we know our data?
Different studies and denominators

Numbers are n/N for treatment groups, non-vertebral fracture

Study	NICE	DTH	Cochrane
Bone	9/93	**?**	**?**
Black 1996	122/1022	122/1022	122/1022
Cummings 1998	261/2214	261/2214	261/2214
Liberman 1995	45/**597**	45/**500**	45/**597**
Lindsay	15/214	**?**	**?**
Pols 1999	19/**950**	19/**792**	19/**950**
Greenspan 1998	**?**	3/**46**	3/**60**
Ascot Evans 2003	**?**	**?**	0/95

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Issue 2: Metric

How do we summarize results of an MTC?

Usually supplement point estimates and CrIs with "probability of being best"

Let's look at an example of what can happen

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MTC: Relative effects vs. placebo

Treatment	OR[a]	95% CrI	Ranking	Probability of being the best treatment (%)
Zoledronic acid	0.28	0.22-0.35	1	98.9
Ibandronate	0.49	0.32-0.72	2	1.0
Alendronate	0.51	0.41-0.63	3	0.1
Risedronate	0.57	0.44-0.73	4	0.0

[a]OR < 1.0 shows an advantage of treatment over placebo.

Jansen et al, Current Medical Research and Opinion, Vol 25, No. 8, 2009, 1861-1868

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Issue 3: Multiple Endpoints

We typically have more than one efficacy endpoint

Multiple sclerosis: disability, relapses, MRI
Osteoporosis: vertebral, hip, non-vertebral fractures

Question: Do we treat an endpoint or a patient?

Hopefully we're treating patients so we want to know which comparator works best at a patient level

Need to combine endpoints in our MTC

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MTC: Multiple endpoints

	Vertebral fractures			Hip fractures			Non-vertebral-non-hip fractures		
Treatment	OR*	95% CrI	P (Best)	OR*	95% CrI	P (Best)	OR*	95% CrI	P (Best)
Zoledronic acid	0.28	0.22 to 0.35	79.1%	0.59	0.41 to 0.82	46.5%	0.79	0.66 to 0.93	9.0%
Alendronate	0.51	0.41 to 0.63	0.0%	0.63	0.39 to 0.95	36.6%	0.87	0.75 to 1.00	1.0%
Risedronate	0.57	0.44 to 0.73	0.0%	0.84	0.44 to 1.43	10.6%	0.61	0.41 to 0.87	87.1%
Ibandronate	0.49	0.32 to 0.72	0.7%	2.02	0.43 to 6.45	5.4%	1.14	0.78 to 1.60	0.4%
Etidronate	0.45	0.16 to 0.95	20.2%	12.90	0.86 to >25	0.9%	1.18	0.65 to 1.99	2.5%

Jansen et al, Seminars in Arthritis and Rheumatism, Vol 40, No. 4, 2011, 275-284.e2

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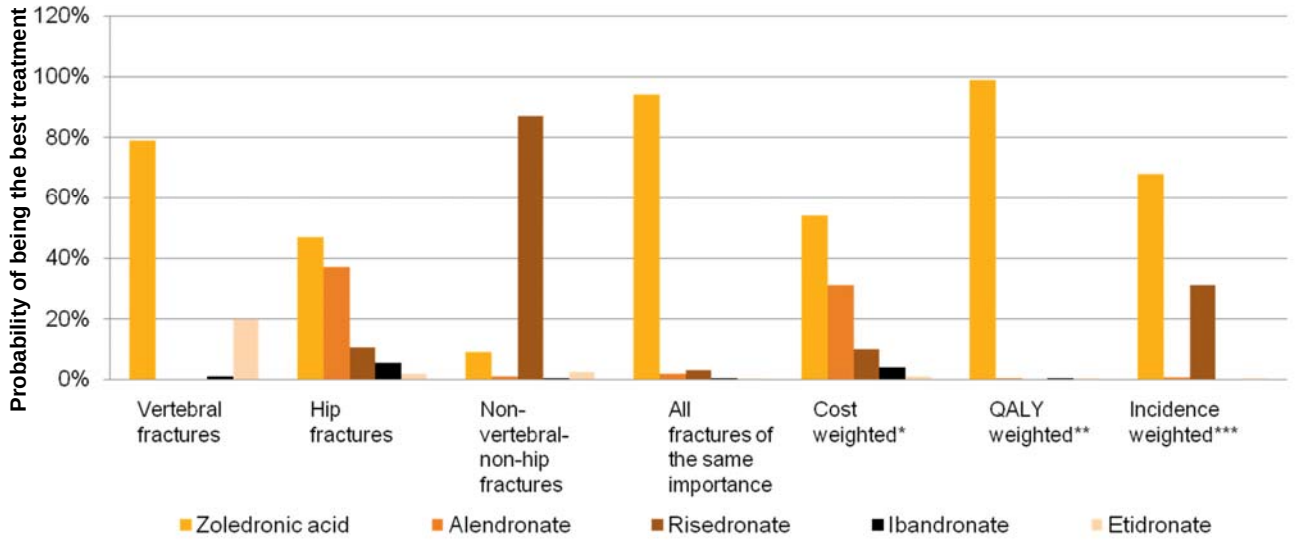
Weighing different endpoints



* Weighted according to event costs: vertebral fractures £539 in the 1st year; hip fractures £7532 in the 1st year; non-vertebral-non-hip fractures £692.
** Weighted according to impact on Quality of life (i.e. utility as measured on a 0 to 1 scale): vertebral fractures 0.626 QALYs in the 1st year; hip fractures 0.792 QALYs in the 1st year; non-vertebral-non-hip fractures 0.886 QALYs.
*** Weighted according to incidence: vertebral fractures 0.0027 events per year; hip fractures 0.0021 events per year; non-vertebral-non-hip fractures 0.0068 events per year.
Sources: Stevenson et al., 2005; Stevenson et al., 2007.

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