



## Issues with Indirect Comparisons

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*Basel Biometrics Society*

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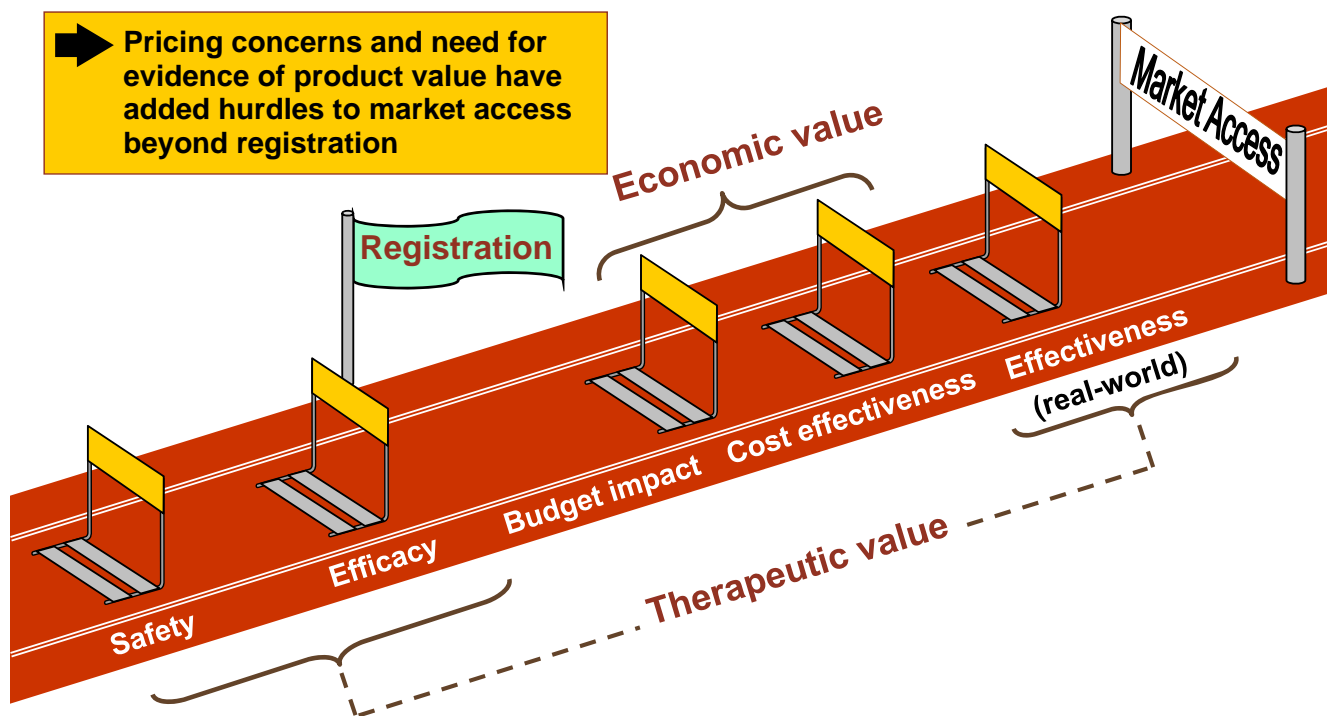


## Agenda

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

# Registration only the first step towards market access



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## What challenges are we facing?

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

**MailOnline**  
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.

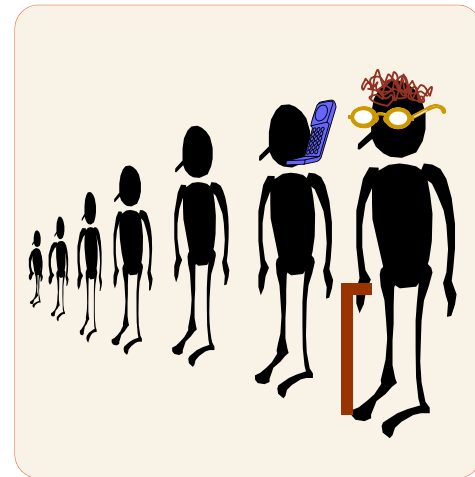
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# Payer Dilemma: not everything is affordable for all patients

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## Limited Resources



## Infinite + Changing Demand

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## Need to show overall value of products

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- 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**



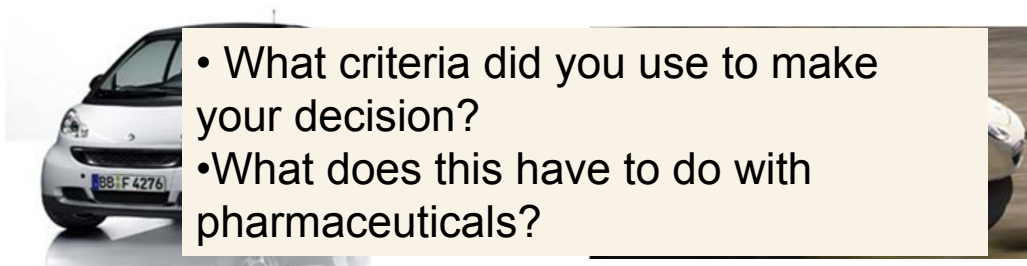
**Lipstick B lasts 24 hours**

**costs €24**



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

## Which one offers better overall value?



- |                                       |                                       |
|---------------------------------------|---------------------------------------|
| ▪ Price: 9,990 EUR                    | ▪ Price: 46,150 EUR                   |
| ▪ Passengers: 2                       | ▪ Passengers: 2                       |
| ▪ Space: 220 – 340 L                  | ▪ Space: 280 L                        |
| ▪ Fuel: 4.3 L/100 km (54mpg)          | ▪ Fuel: 9.4 L/100 km (25mpg)          |
| ▪ CO <sub>2</sub> Emissions: 103 g/km | ▪ CO <sub>2</sub> Emissions: 221 g/km |
| ▪ Airbags: 2                          | ▪ Airbags: 2                          |
| ▪ 0 – 100 km/h in 16.7 sec            | ▪ 0 – 100 km/h in 5.9 sec             |
| ▪ Fun factor: X                       | ▪ Fun factor: >>X                     |

# Reconsider the criteria...



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

Cost

Efficacy

Safety

QoL



- Price: 46,150 EUR

- Passengers: 2

Need to combine these criteria to define overall value

- Fuel: 9.1 L/100 km (25mpg)

- CO<sub>2</sub> Emissions: 221 g/km

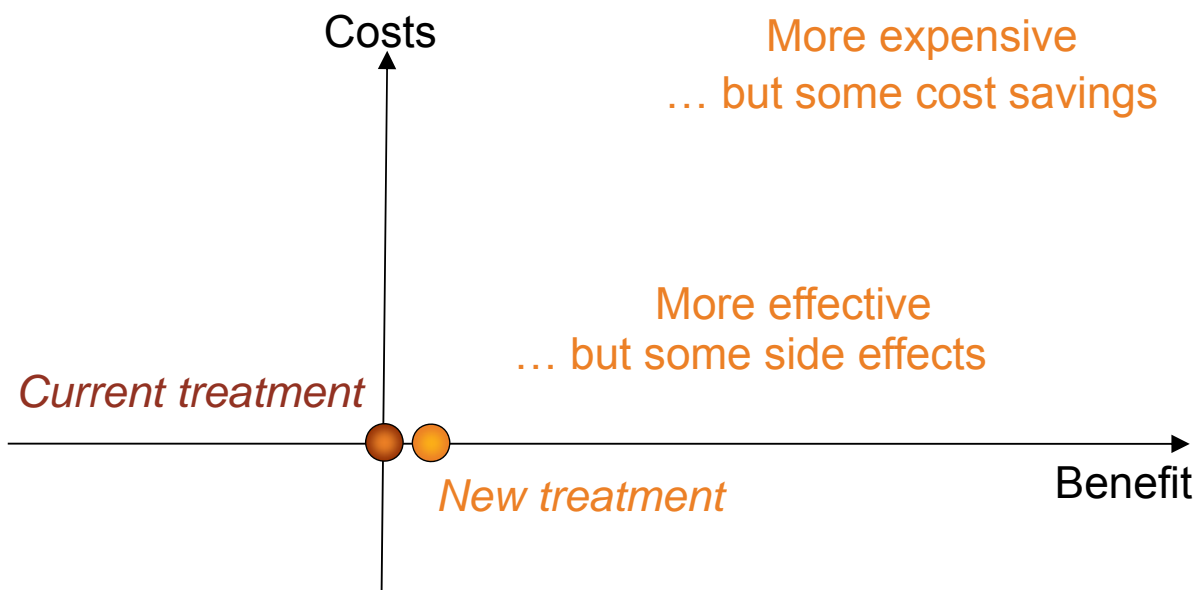
- Airbags: 2

- 0 – 100 km/h in 5.9 sec

- Fun factor: >>X

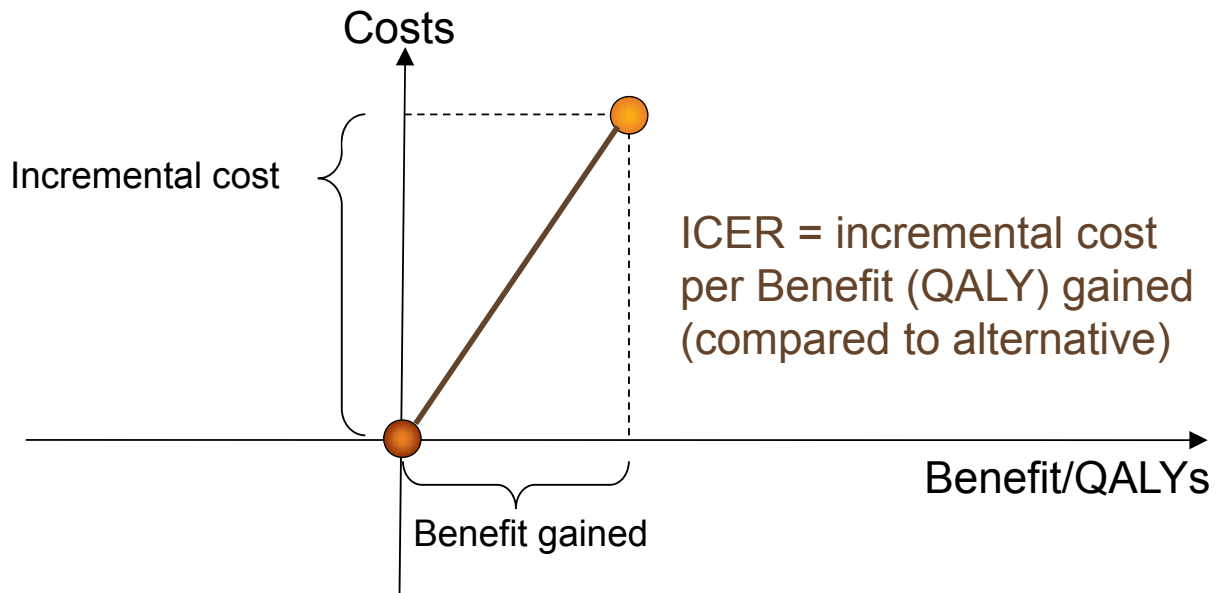
## Trading off benefits, harms and costs

How do you get cost/benefit?



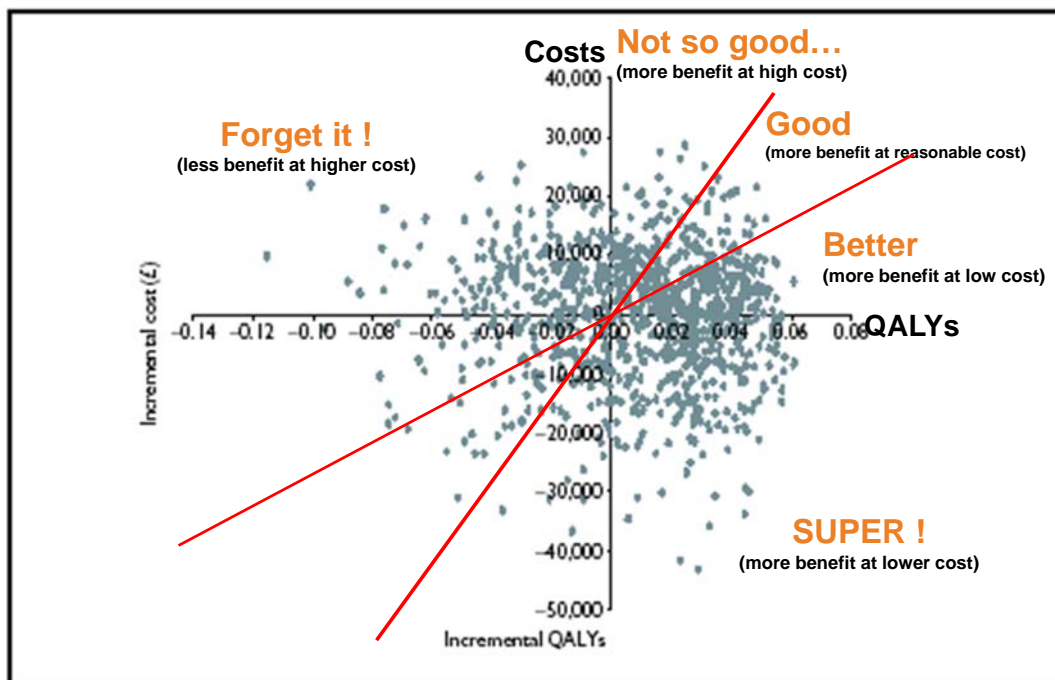
# Cost Effectiveness is a technique for quantifying overall value

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



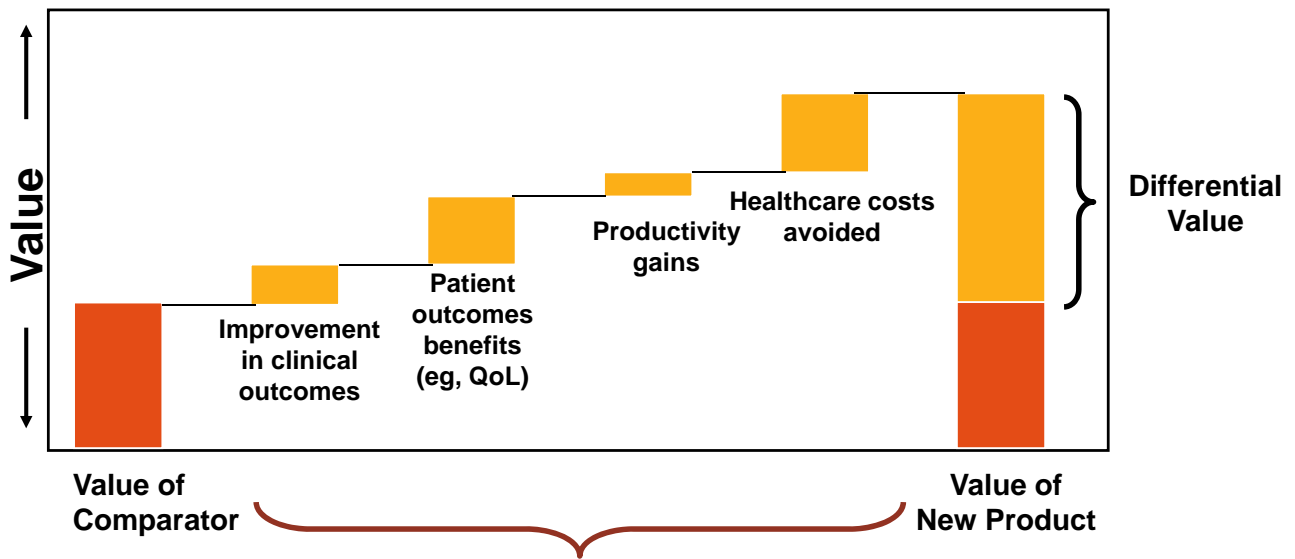
# Cost-effectiveness: Tool for decision making

*Good overall value?*



# Demonstrating Differential Value of our Products

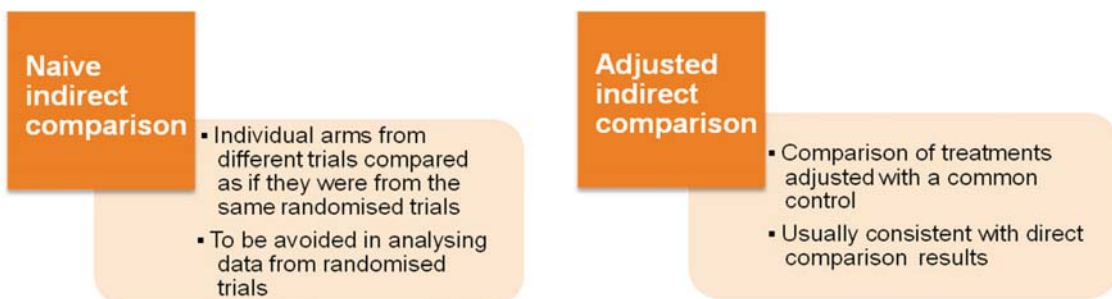
## Ideal Scenario



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

## 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



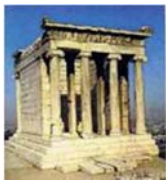
### Basic assumptions underlying indirect comparisons:

**Homogeneity assumption-**  
for standard meta-analysis

**Similarity assumption-**  
for adjusted indirect comparison

**Consistency assumption-**  
for the combination of direct and indirect evidence

# Simple Comparison



Athena Nike

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Parthenon

Athena Nike smaller than Parthenon

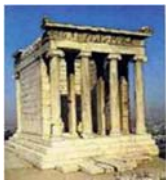


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Poseidon at Sounion

Parthenon smaller than Poseidon at Sounion



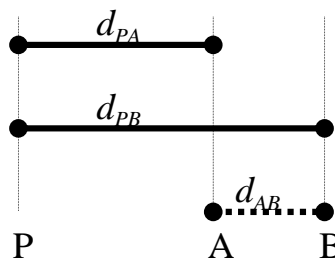
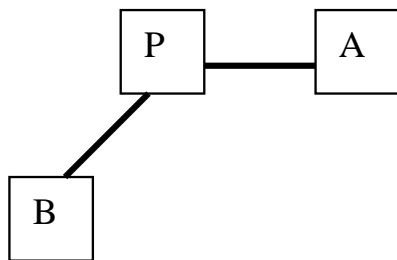
?



$A < B, B < C \rightarrow A < C$   
Therefore, Nike smaller than Poseidon

**Easy comparison because we can measure directly**

# Indirect comparison – simple case



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

# 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?

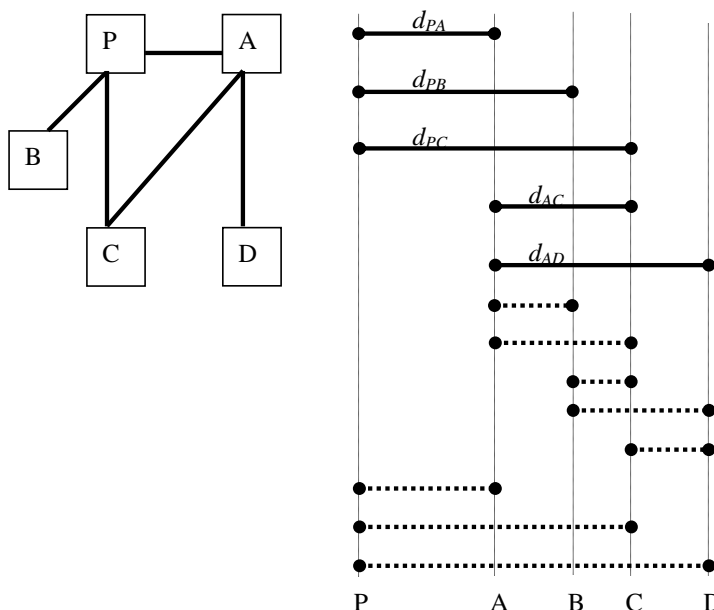
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# Standard Methods for making Indirect Comparisons

- 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

## Mixed Treatment Comparisons



# 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...

## 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/ <b>597</b>	45/ <b>500</b>	45/ <b>597</b>
Lindsay	15/214	?	?
Pols 1999	19/ <b>950</b>	19/ <b>792</b>	19/ <b>950</b>
Greenspan 1998	?	3/ <b>46</b>	3/ <b>60</b>
Ascot Evans 2003	?	?	0/95

## Issue 2: Metric

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How do we summarize results of an MTC?

Usually supplement point estimates and Crls with “probability of being best”

Let’s look at an example of what can happen

## MTC: Relative effects vs. placebo

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Treatment	OR <sup>a</sup>	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

<sup>a</sup>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

## 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

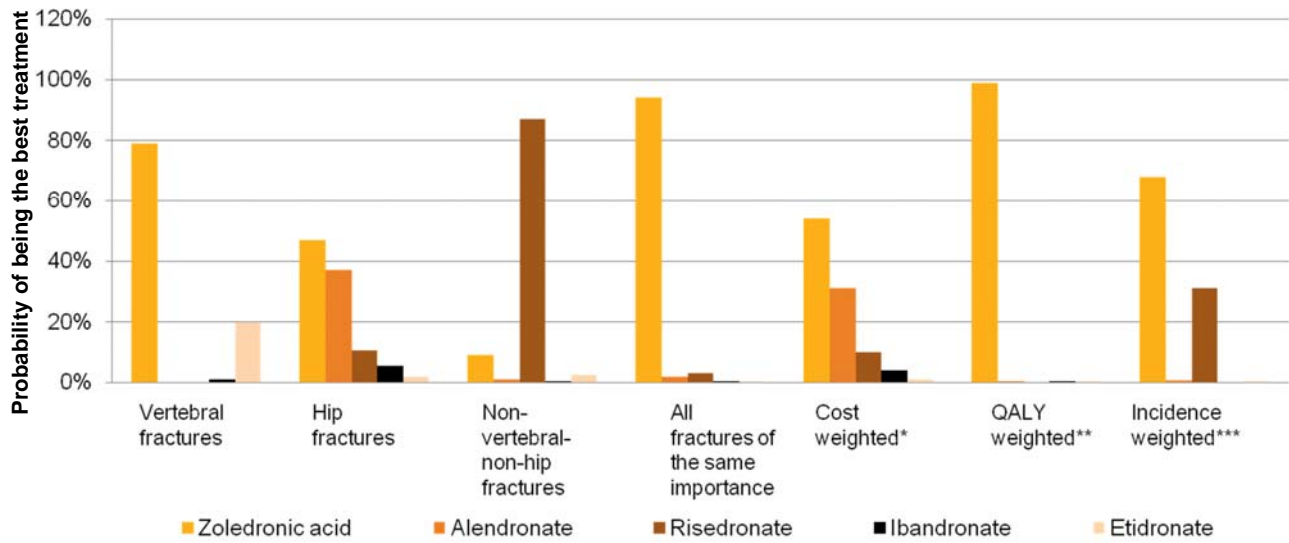
Need to combine endpoints in our MTC

## MTC: Multiple endpoints

Treatment	Vertebral fractures			Hip fractures			Non-vertebral-non-hip fractures		
	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

# 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 QALY's in the 1st year, hip fractures 0.792 QALY's in the 1st year, non-vertebral-non-hip fractures 0.886 QALY's.

\*\*\* 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.

