

Bayesian re-analyses of Health Technology Assessments: evaluation of modelling assumptions

Jaime Peters, Keith Abrams,
Alex Sutton, Nicola Cooper, David Spiegelhalter

Peninsula Medical School, Universities of Exeter and Plymouth, UK
Department of Health Sciences, University of Leicester, UK
MRC Biostatistics Unit, Cambridge, UK

Health Technology Assessment (HTA)

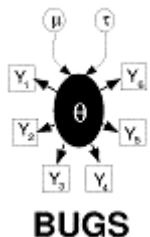
- Assess clinical and cost-effectiveness evidence on drugs and devices
- Identification and review of relevant evidence
 - Systematic review methods
- Synthesis of evidence
 - Meta-analysis methods
- Decision-making under uncertainty
- UK: National Institute for Health and Clinical Excellence (NICE)
“rational decision-making”

Bayesian methods of analysis

- Explicit inclusion of external evidence
 - Incorporation of related evidence
 - Incorporation of prior evidence/opinion
 - E.g. informed, sceptical, enthusiastic, vague (non-informative)

- Uncertainty: Inclusion and propagation throughout model
- Flexibility: synthesis of diverse and complex evidence (WinBUGS software)

- Direct probability statements, e.g. 60% probability that treatment A is the best treatment
- Predictive distributions



$$P(\theta | Data) \propto P(\theta)P(Data | \theta)$$



HTA case study: drug-eluting stents (DES) in percutaneous coronary intervention (Hill et al 2007)

Control stents
Bare metal stents (BMS)

Vs.

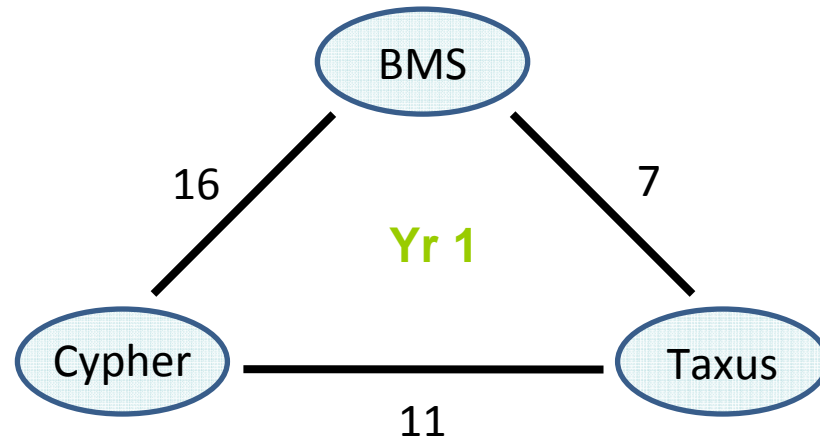
'Active' stents
Drug-eluting stents (DES)
= Cypher & Taxus

Outcome: Reduction in target lesion revascularisation (TLR) within 1 yr of initial procedure

	Used in HTA	Available data	Bayesian approach
Modelling approach	Deterministic	Stochastic	Full parameter uncertainty propagated through model
Staged approach to cost-effectiveness	Two-stage approach	One-stage comprehensive approach, allowing uncertainty and maintaining any correlation throughout the model	
Clinical effectiveness – evidence synthesis	Pairwise (DES vs BMS)	Cypher vs Taxus vs BMS	MTC – not nec Bayesian (flexible)
Individual	year “estimated benefit stable over long term”	(still clinically important after 1 yr)	Random Walk MTC (flexible)

Probabilistic sensitivity analysis not yet standard approach
- uncertainty in resultant ICERs often unknown

Treatment comparisons



BASKET trial: BMS vs Cypher vs Taxus

Evidence synthesis: assumptions

Pairwise synthesis – random effects meta-analysis

- BMS vs Cypher
- BMS vs Taxus
- BMS vs Cypher + Taxus (Approach taken in published HTA)
- BASKET trial: BMS vs Cypher vs Taxus

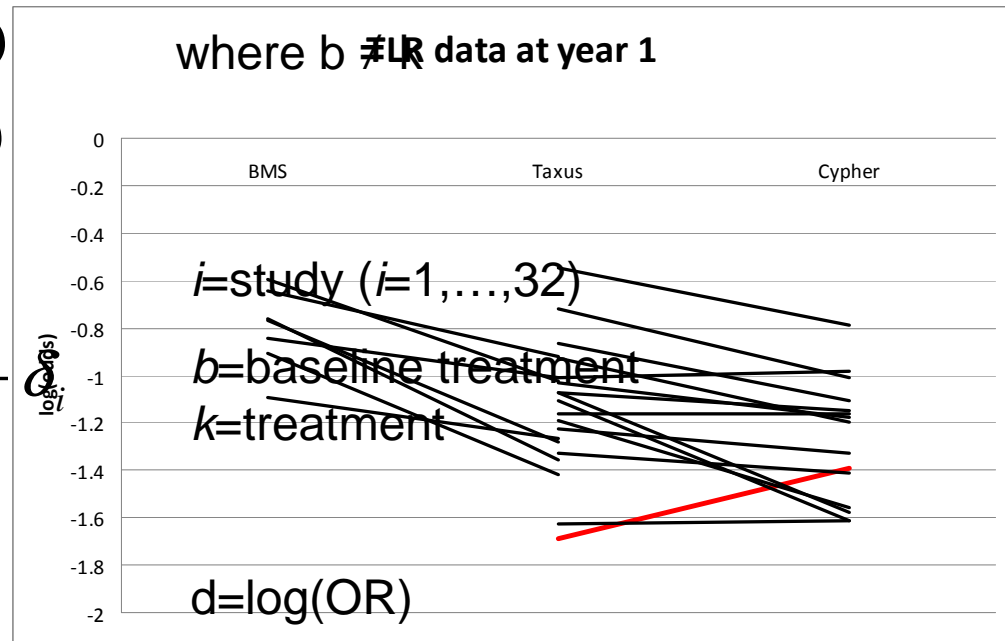
$$r_{bi} \sim \text{bin}(p_{bi}, n_{bi})$$

$$r_{ki} \sim \text{bin}(p_{ki}, n_{ki})$$

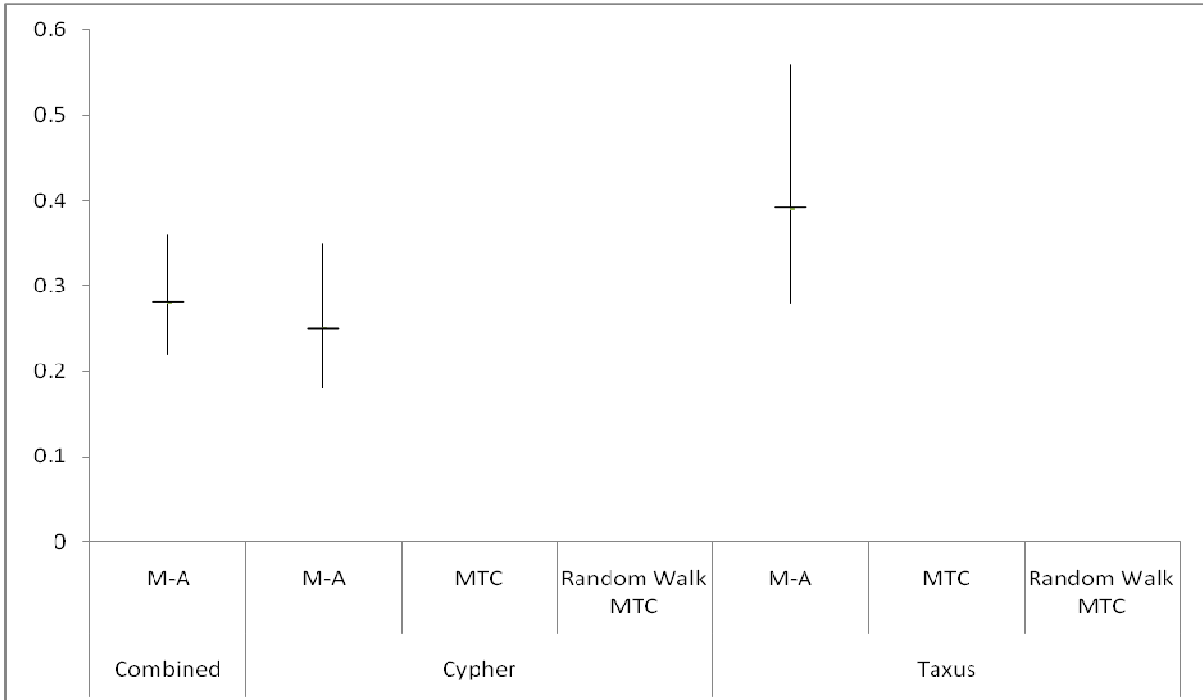
$$\text{logit}(p_{bi}) = \mu_i$$

$$\text{logit}(p_{ki}) = \mu_i + \delta_i$$

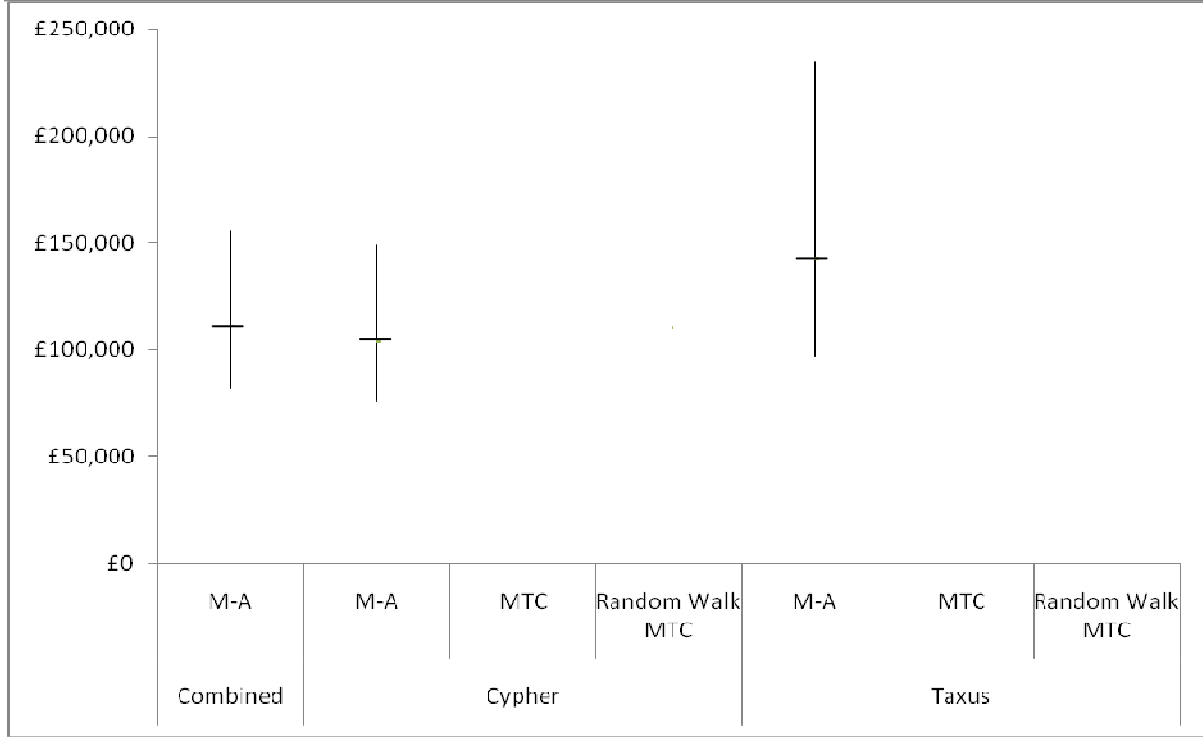
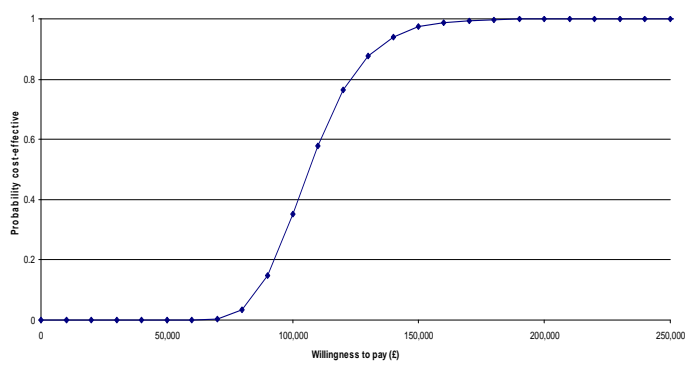
$$\delta_i \sim N(d, \tau^2)$$



Pooled clinical effectiveness estimates



Incremental cost-effectiveness estimates



Evidence synthesis: assumptions

Standard Mixed Treatment Comparison

- Using direct and indirect evidence: information from Cypher vs Taxus
- Assume consistency within study comparisons and between study comparisons
- Correlation of BASKET trial accounted for

$$r_{bi} \sim \text{bin}(p_{bi}, n_{bi})$$

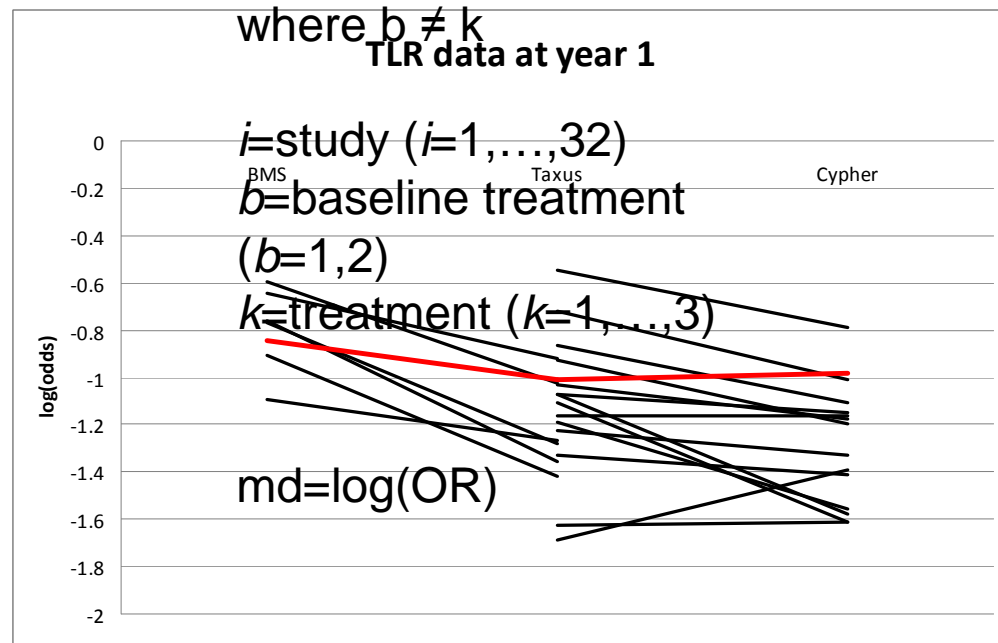
$$r_{ki} \sim \text{bin}(p_{ki}, n_{ki})$$

$$\text{logit}(p_{bi}) = \mu_i$$

$$\text{logit}(p_{ki}) = \mu_i + \delta_i$$

$$\delta_i \sim N(md, \tau^2)$$

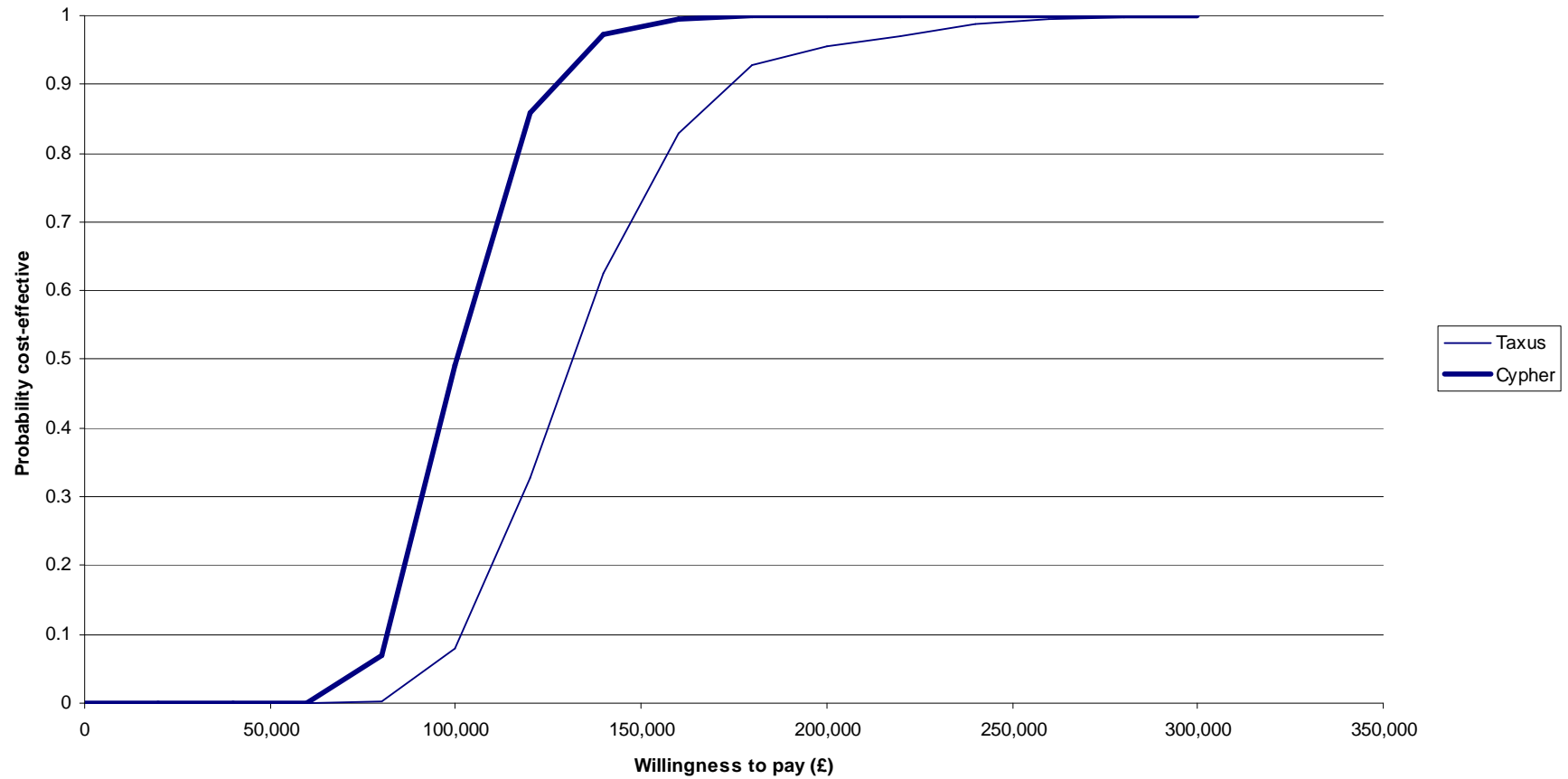
$$md = d_k - d_b$$



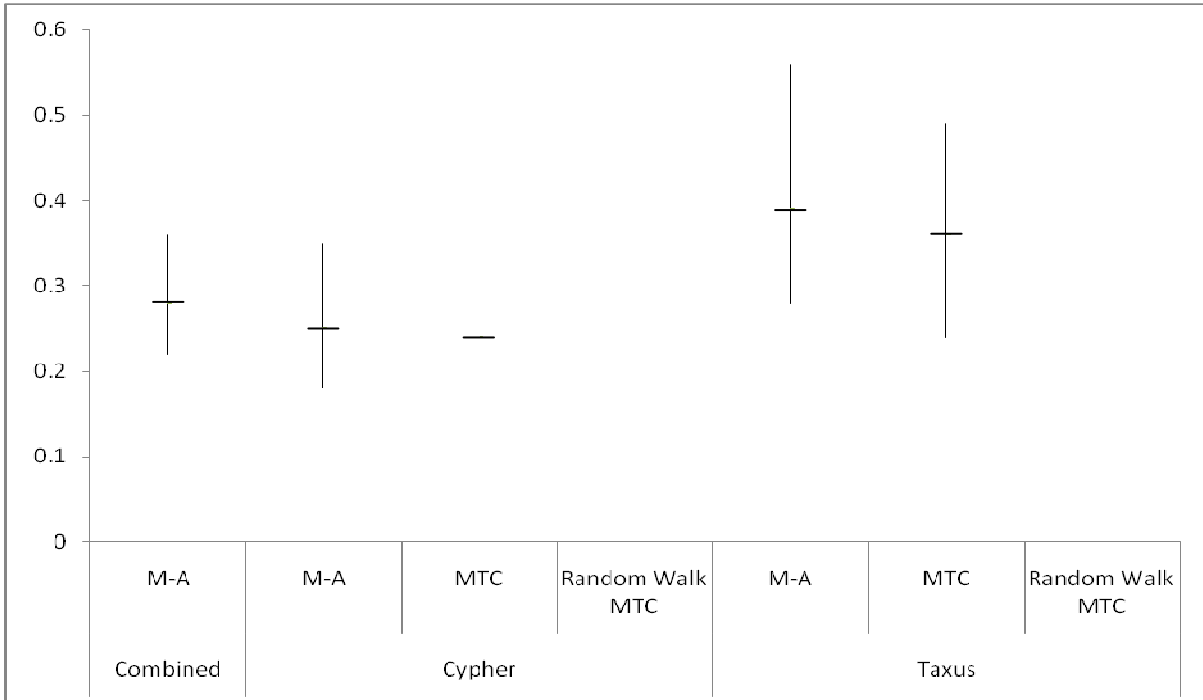
Pr(Taxus is best stent) = 3%

Pr(Cypher is best stent) = 97%

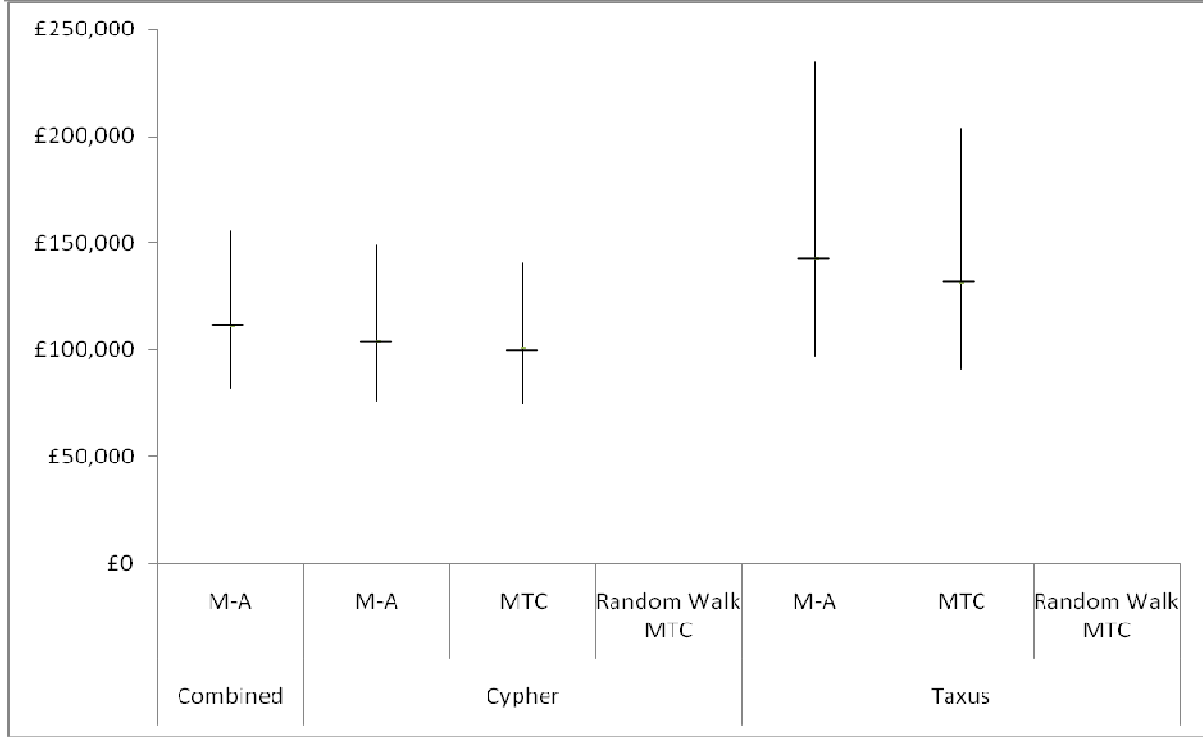
Standard Mixed Treatment Comparison



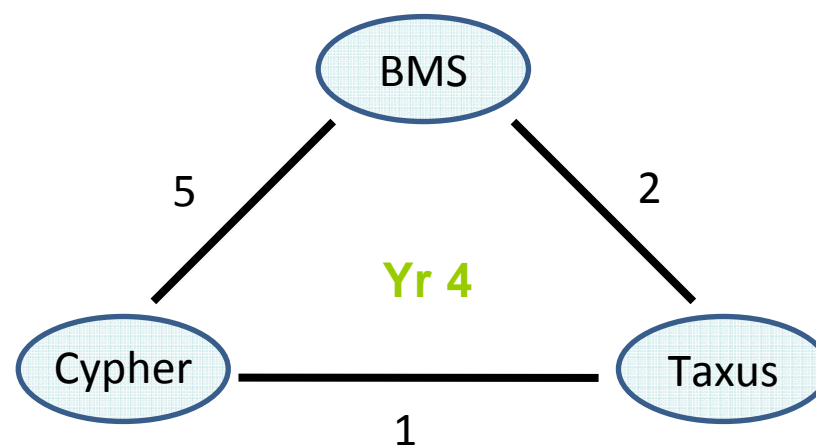
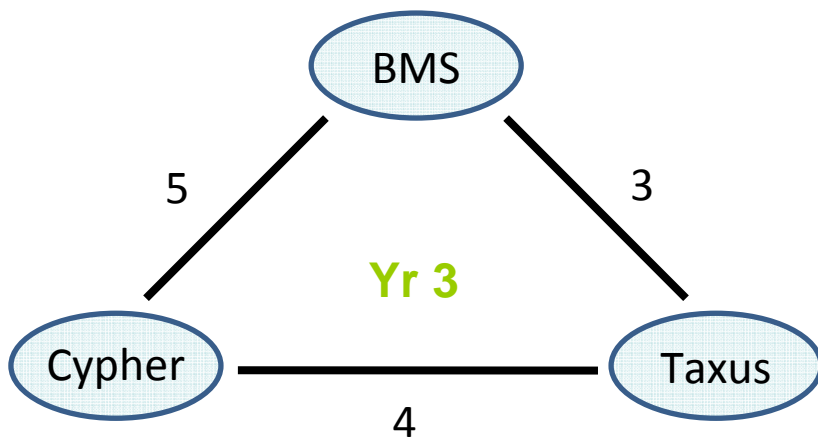
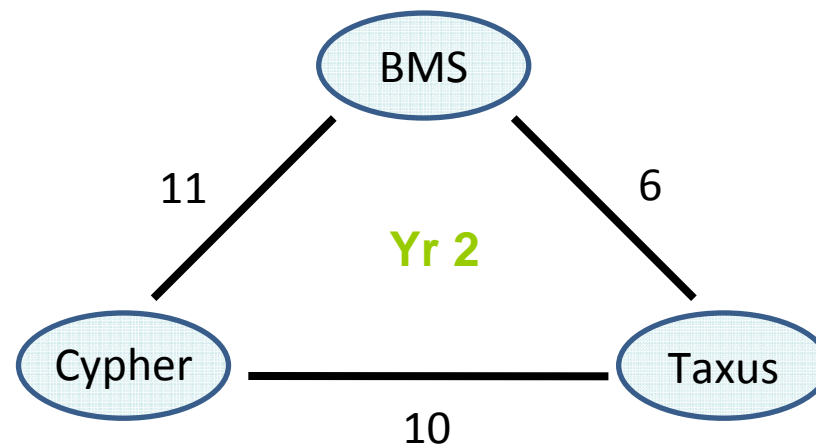
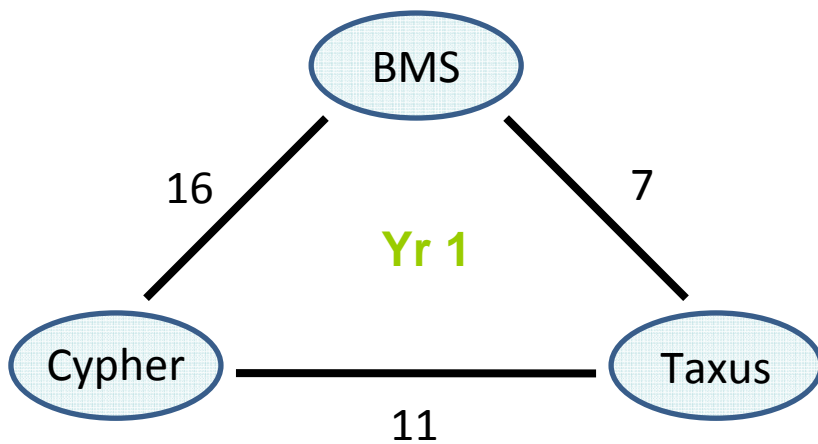
Pooled clinical effectiveness estimates



Incremental cost-effectiveness estimates



Treatment comparisons



Evidence synthesis: assumptions

Random Walk Mixed Treatment Comparison

- Allows incorporation of evidence at different time-points
 - no new studies, but more evidence
- Assumes estimate at time t is more similar to that at t-1, than t-2 etc..
- Assumes proportional hazards

$$r_{biu} \sim \text{bin}(p_{biu}, n_{biu})$$

$$r_{kiu} \sim \text{bin}(p_{kiu}, n_{kiu})$$

$$\log \text{it}(p_{biu}) = \mu_i + \theta_u + \varphi_{iu}$$

$$\log \text{it}(p_{kiu}) = \mu_i + \theta_{iu} + \varphi_{iu} + \delta_{ibku}$$

$$\delta_{ibk1} \sim N(md, \tau_{bk}^2)$$

$$\delta_{ibku} \sim N(\delta_{ibk1}, \tau_{RW}^2)$$

$$md = d_k - d_b$$

where $b \neq k$

i =study ($i=1, \dots, 32$)

b =baseline treatment ($b=1, 2$)

k =treatment ($k=1, \dots, 3$)

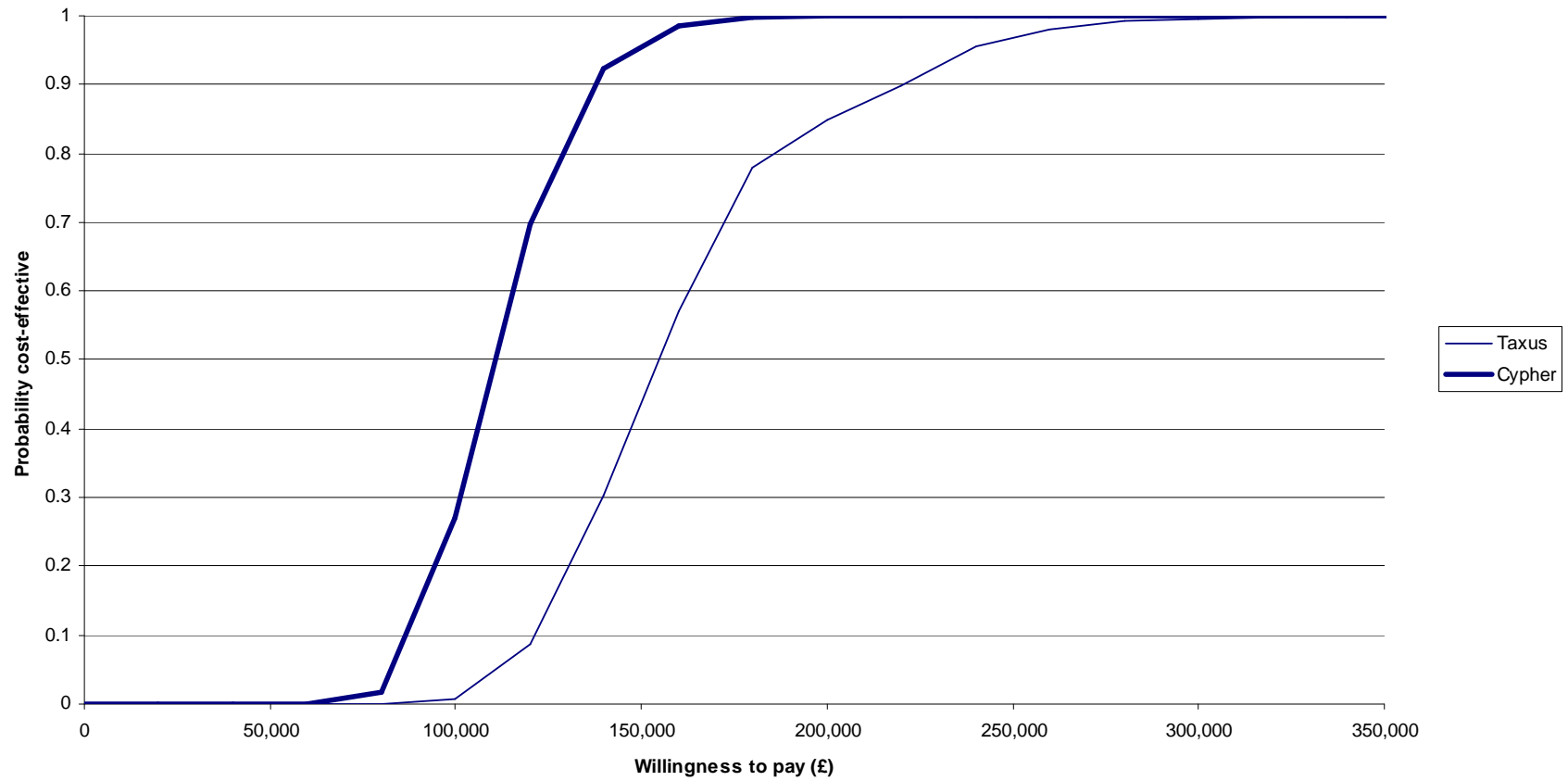
u =time segment ($u=1, \dots, 4$)

md = $\log(\text{HR})$

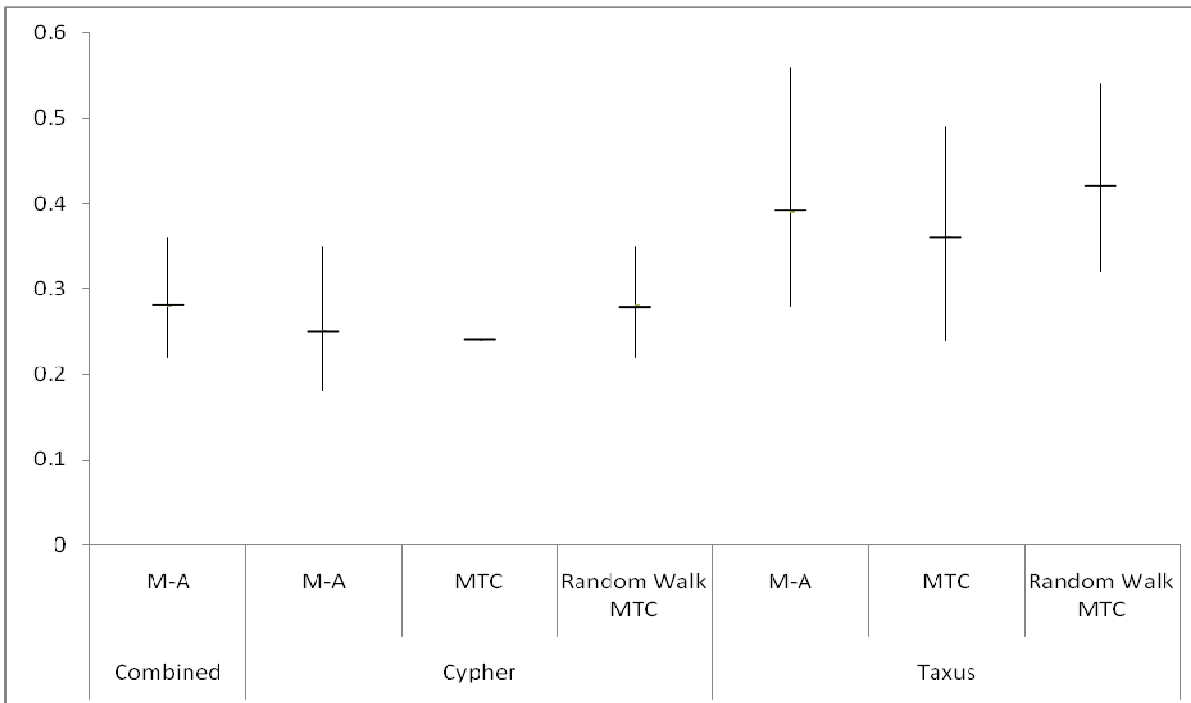
Pr(Taxus is best stent) < 1%

Pr(Cypher is best stent) > 99%

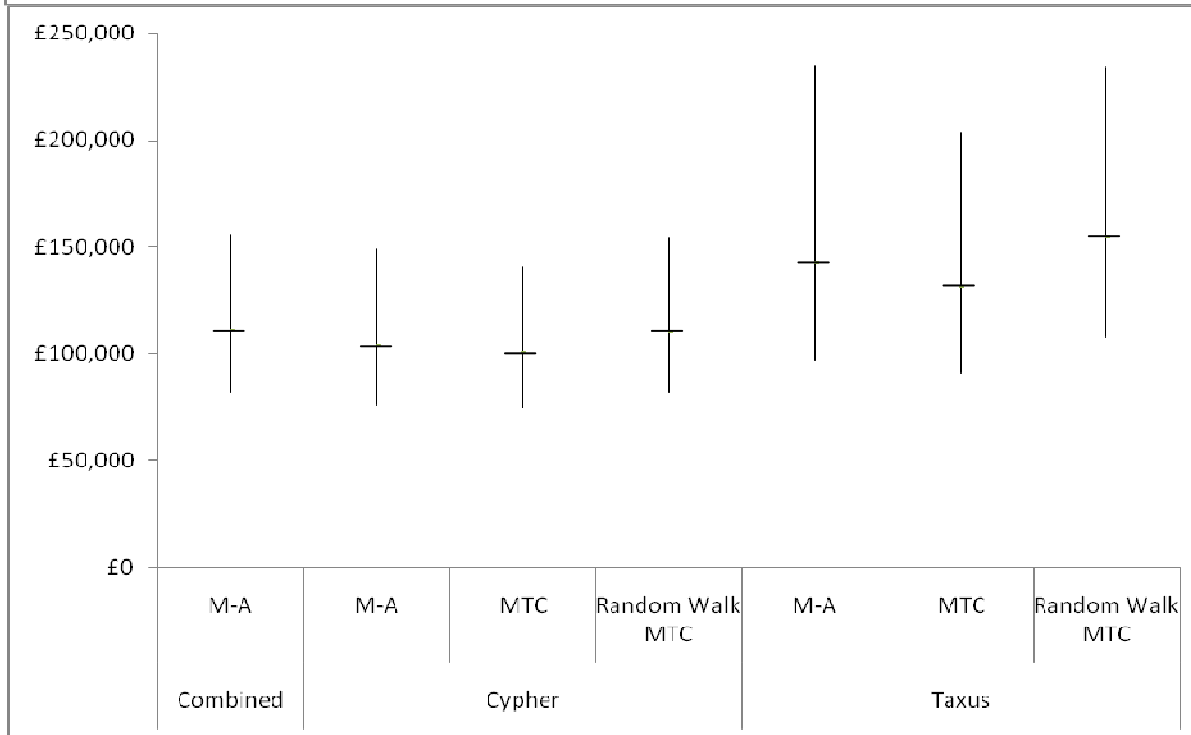
Random Walk Mixed Treatment Comparison



Pooled clinical effectiveness estimates



Incremental cost-effectiveness estimates



Drug-eluting stents results

- MTC reduces uncertainty of estimates
- Little qualitative difference in findings
- Interpretation of results from different methods = different outcome for the cost-effectiveness modelling
 - 1 yr repeat procedure
 - HR across 4 years of data from random walk MTC
 - Question changes
- Little impact on findings of 4 year data, agreeing with assumption that effect “stable over long term” in HTA report
- Use of all relevant evidence
- Findings specific to particular HTA – mixed findings from use of different evidence synthesis methods for re-analysis of two further HTAs (unpublished results)

Other areas of potential

- Explicit incorporation of external information
 - Expert opinion

On-going work at Exeter - local HTA and decision-making. Lack of effectiveness and cost evidence

Aim: elicit likely scenarios from experts,
model all scenarios

- Would any scenarios lead to drug/device being cost-effective?
- How likely are such scenarios?

Other areas of potential

- Explicit incorporation of external information
 - Expert opinion
- Addressing biases and uncertainty
 - Individual studies: internal and external bias (Turner et al)
 - Model structure uncertainty (Jackson et al: model-averaging)
- Estimation of sub-group effects
- Modelling inconsistently measured and reported studies
- Full decision theoretic approach – expected value of information

Practical use of Bayesian methods in HTA

- Computational issues: Excel vs WinBUGS
 - Coding and convergence
 - Additional time
 - Error checking
- Increased understanding and acceptance of Bayesian methods in general
- But in NICE methods guidance
 - Pairwise comparison, justify use of MTC, but use “all relevant evidence”
 - How to define “all relevant evidence”?
 - No mention of Bayesian methods

Acknowledgements

- Monica Lai, Sylwia Bujkiewicz – Leicester, UK
- Peter Juni, Simon Wandel – Berne, Switzerland
- Jo Richardson – NICE, UK
- Adrian Bagust – Liverpool, UK

References

- Hill et al 2007 drug-eluting stents: a systematic review and economic evaluation. *Health Technology Assessment*, 11(46).
- Jackson et al 2009 Accounting for uncertainty in health economic decision models by using model averaging. *J RSS A*, 172:383-404.
- Lu & Ades 2004 Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*, 23: 3105-3124.
- Lu et al 2007 Meta-analysis of mixed treatment comparisons at multiple follow-up times. *Stat Med*, 26:3681-3699.
- Spiegelhalter D et al 2003 WinBUGS user manual: Version 1.4, MRC Biostatistics Unit, Cambridge
- Stettler et al 2008 Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. *BMJ*, 337:a1331.
- Turner et al 2009 Bias modelling in evidence synthesis. *J RSS A*, 172:23-49