Comparative efficacy and effectiveness via meta-analysis – Health economics approach

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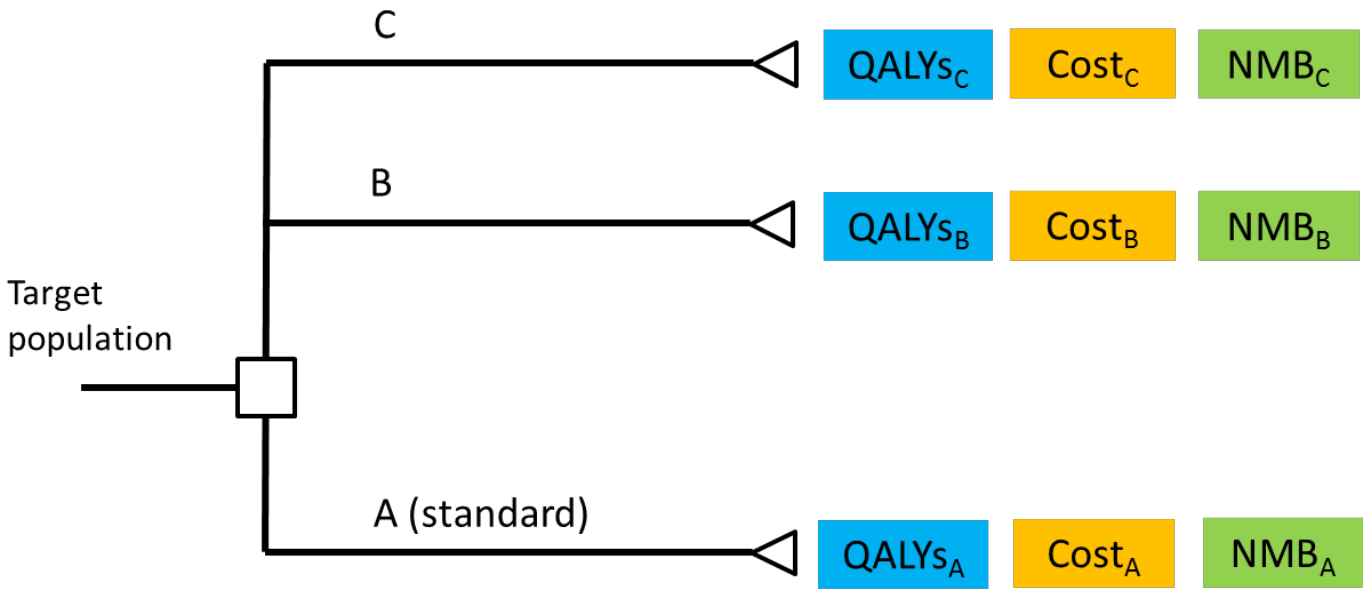
Cost-effectiveness analysis



NMB= QALYs * WTP - Costs

Decision modeling for cost-effectiveness analysis

- An individual study hardly ever provides information regarding all aspects informing the cost-effectiveness decision of the competing interventions
- Decision models are mathematical frameworks that integrate relevant evidence and provide estimates of resource use and outcomes associated with competing interventions

Decision modeling: Evidence synthesis & extrapolation

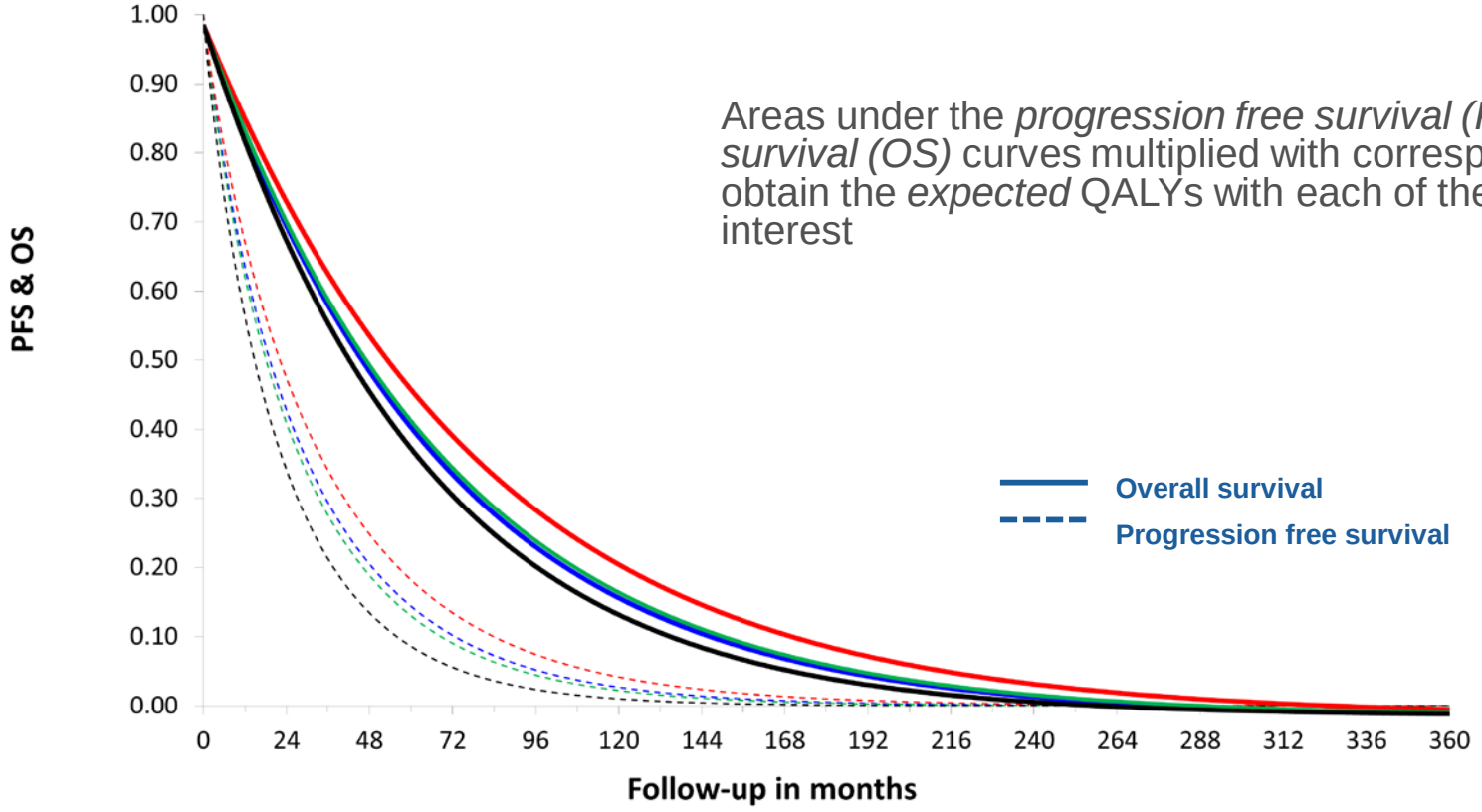
- Evidence synthesis
  - Relative treatment effects over time
  - Outcomes over time with standard of care / natural history
  - Relationship between surrogate and clinical endpoints
  - Relationship between clinical and economic endpoints

- Extrapolation
  - beyond the time horizon, interventions, outcomes, and settings observed in the available individual studies

Example research question

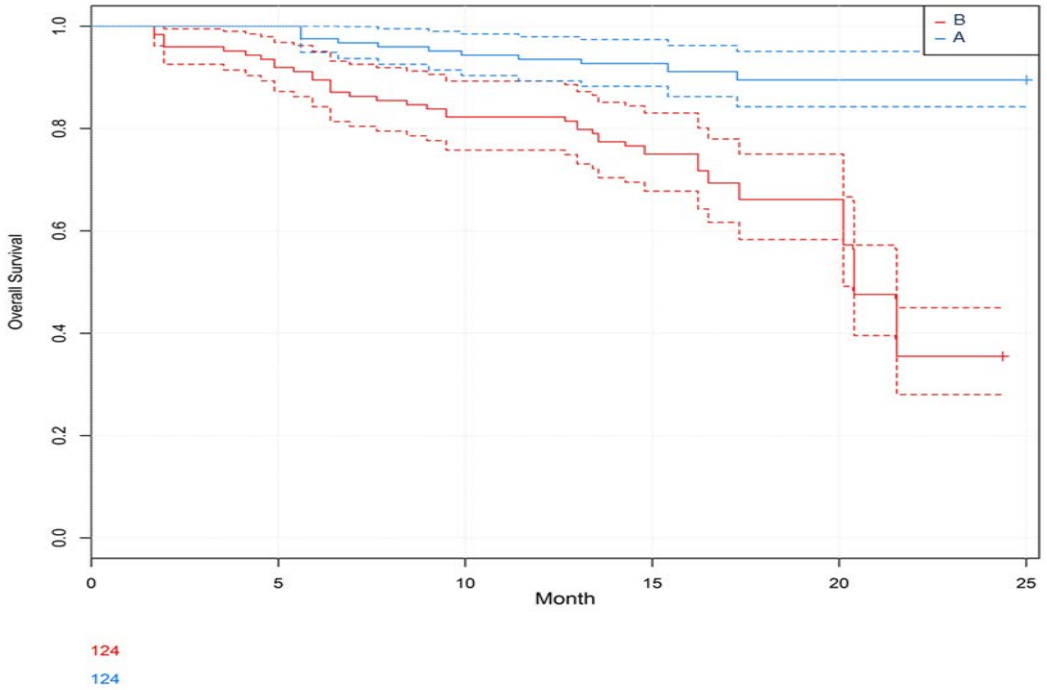
What is the cost-effectiveness of available interventions for the xth line treatment of tumor type y?

This is what we want: comparative effectiveness estimates



Areas under the *progression free survival (PFS)* and *overall survival (OS)* curves multiplied with corresponding utilities to obtain the *expected* QALYs with each of the interventions of interest

This is what we have

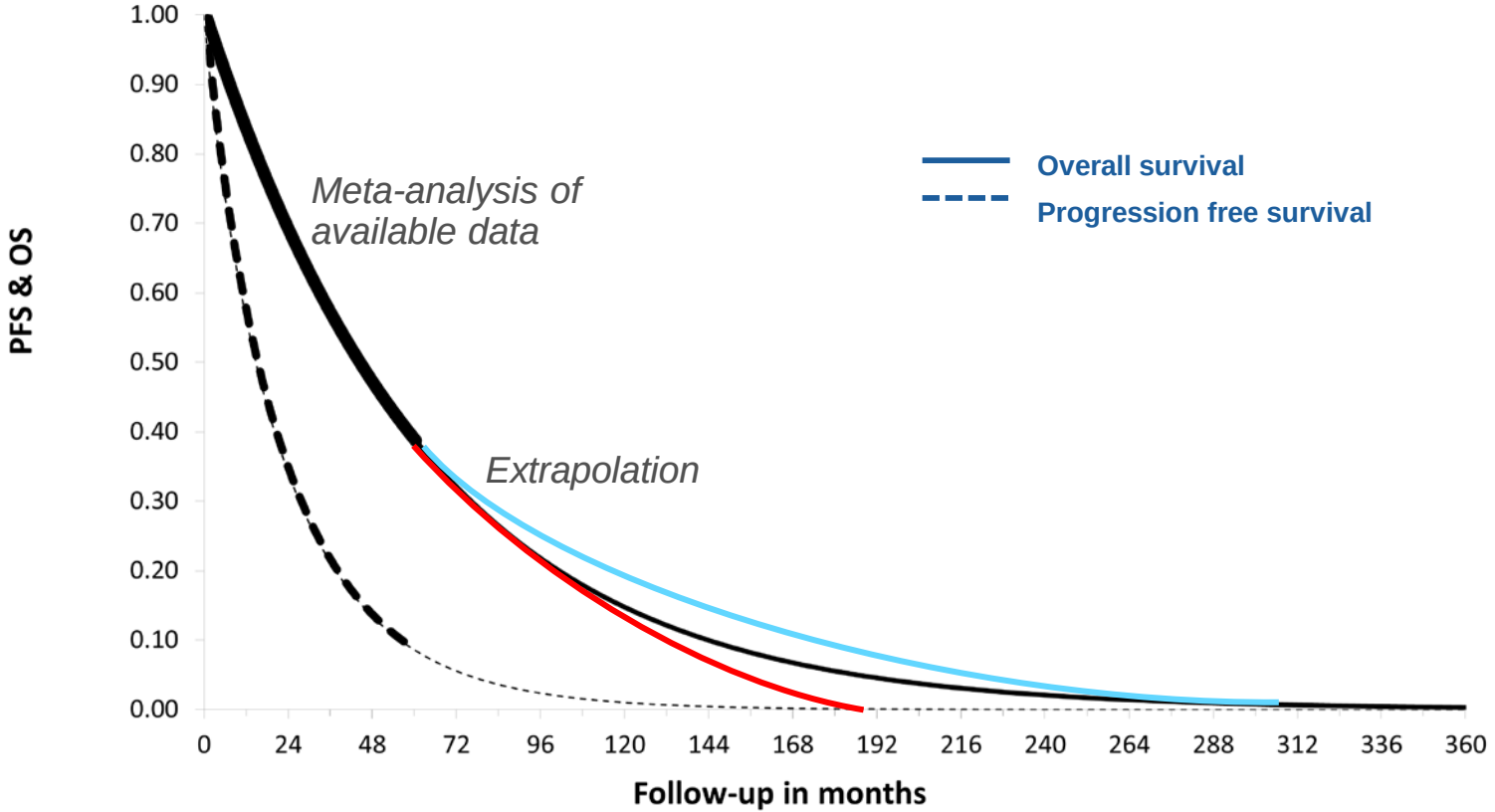


- *A set of randomized controlled trials each comparing a subset of the interventions of interest*
- *Limited follow-up (15-50 months)*

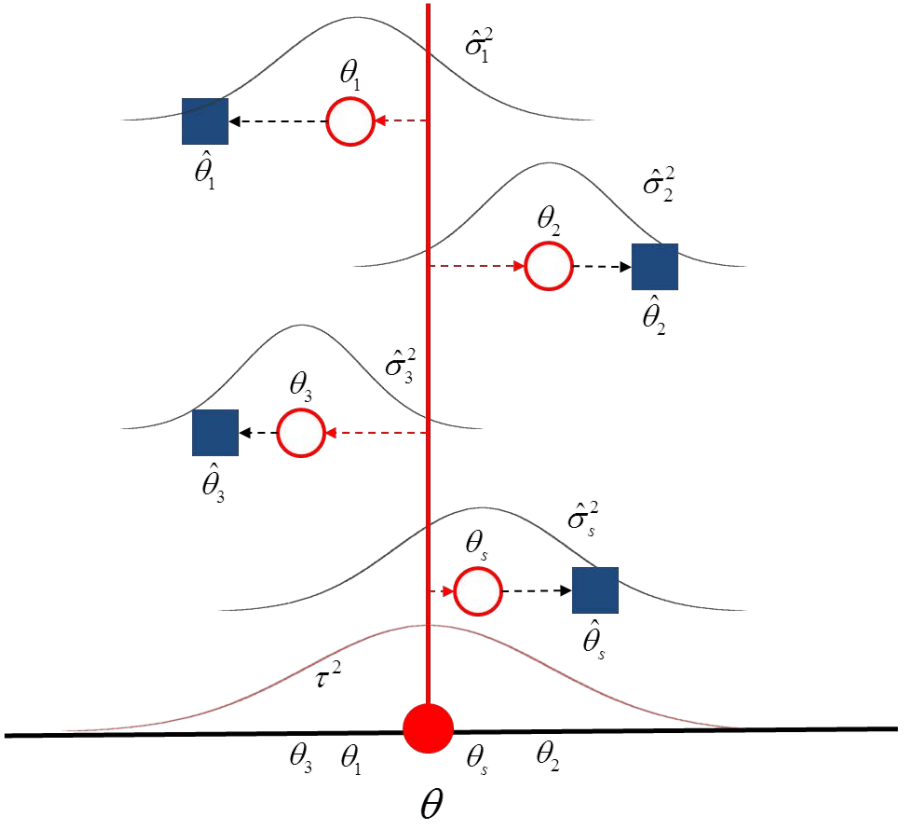
Steps

1. Meta-analysis of *absolute effect* with reference treatment A; “real-world” data
2. *Network meta-analysis* to obtain *relative treatment effects* for each intervention relative to A; randomized controlled trials
3. Extrapolation of 1 and 2 over time
4. Apply extrapolated relative treatment effects to extrapolated absolute effect of A to obtain absolute effects for all interventions

Baseline model



Meta-analysis - random effects model



$$\hat{\theta}_s \sim Normal\left(\theta_s, \hat{\sigma}_s^2\right)$$

$$\theta_s \sim Normal\left(\theta, \tau^2\right)$$

Baseline model – meta-analysis of parametric survival functions

- Weibull

$$\ln\left(h_s\left(t\right)\right) = \theta_{0,s} + \theta_1 \ln\left(t\right)$$

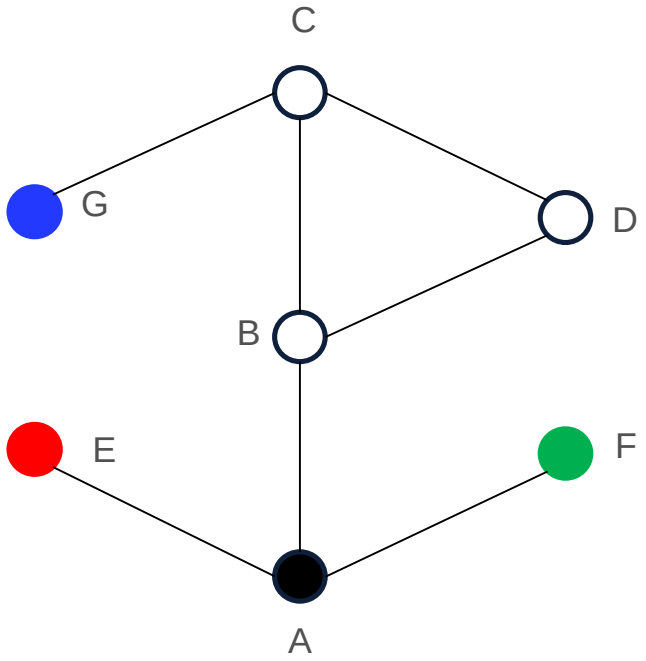
$$\theta_{0,s} \sim Normal\left(\theta_0, \tau^2\right)$$

- Fractional polynomial

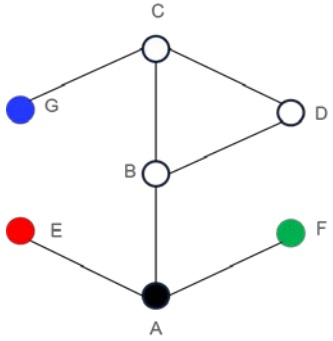
$$\ln\left(h_s\left(t\right)\right) = \begin{cases} \theta_{0,s} + \theta_1 t^{p_1} + \theta_2 t^{p_2} & p_1 \neq p_2 \\ \theta_{0,s} + \theta_1 t^{p} + \theta_2 t^{p} \ln\left(t\right) & p = p_1 = p_2 \end{cases} \quad \text{with } t^0 = \ln\left(t\right)$$

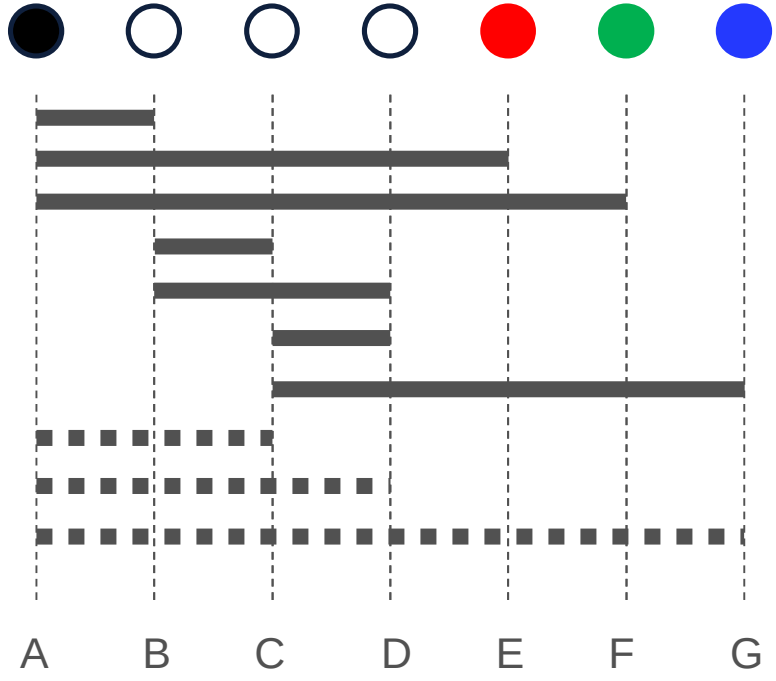
$$\theta_{0,s} \sim Normal\left(\theta_0, \tau^2\right)$$

Network meta-analysis for relative treatment effects



Network meta-analysis for relative treatment effects





$$d_{bk} = d_{Ak} - d_{Ab}$$

Assumption: No differences in effect-modifiers between studies indirectly compared

direct comparison
indirect comparison

Network meta-analysis for relative treatment effects

$$\hat{\delta}_{sa} \sim Normal\left(\delta_{sa}, \hat{\sigma}_{sa}^{2}\right)$$

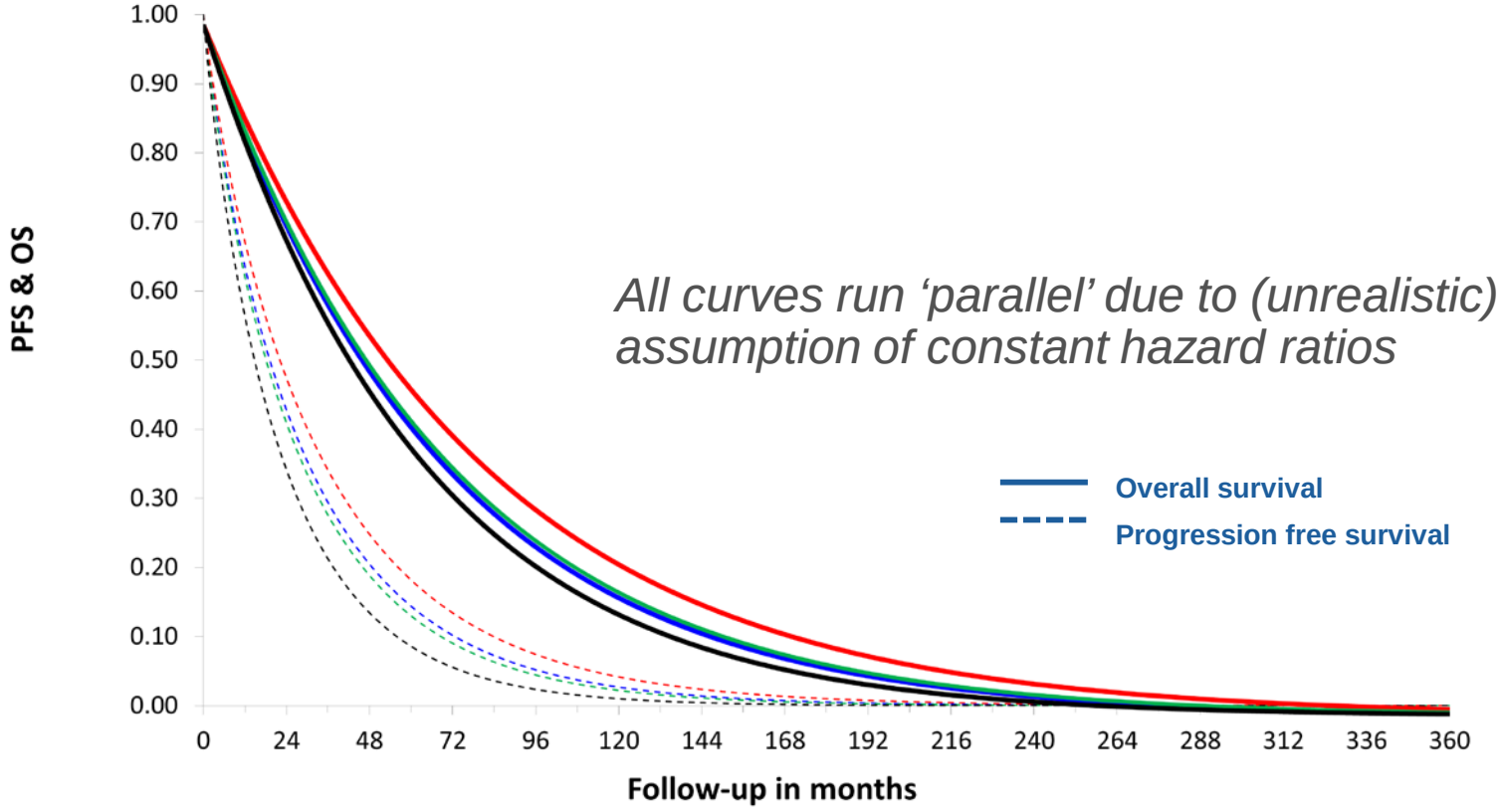
$$\delta_{sa} \sim Normal\left(d_{1k_{sa}} - d_{1k_{s1}}, \tau^{2}\right)$$

Network meta-analysis for relative treatment effects

A	**0.22 (0.11 - 0.45)**	0.32 (0.13 - 0.8)	0.44 (0.2 - 0.96)	**1.26 (1.01 - 1.58)**	1.11 (0.93 - 1.33)	1.09 (0.78 - 1.52)
4.47 (2.25 - 8.89)	B	1.44 (0.78 - 2.66)	**1.95 (1.31 - 2.89)**	5.66 (2.75 - 11.58)	4.98 (2.45 - 10.1)	4.85 (2.28 - 10.43)
3.09 (1.25 - 7.66)	0.69 (0.38 - 1.28)	C	1.35 (0.69 - 2.63)	3.91 (1.55 - 9.96)	3.45 (1.37 - 8.67)	**3.35 (1.28 - 8.83)**
2.30 (1.05 - 5.06)	**0.51 (0.35 - 0.76)**	0.74 (0.38 - 1.45)	D	2.90 (1.28 - 6.55)	2.56 (1.14 - 5.76)	2.49 (1.06 - 5.89)
0.79 (0.63 - 0.99)	0.18 (0.09 - 0.36)	0.26 (0.1 - 0.64)	0.34 (0.15 - 0.78)	E	0.88 (0.66 - 1.17)	0.86 (0.57 - 1.29)
0.90 (0.75 - 1.07)	0.20 (0.1 - 0.41)	0.29 (0.12 - 0.73)	0.39 (0.17 - 0.88)	1.13 (0.85 - 1.51)	F	0.98 (0.67 - 1.42)
0.92 (0.66 - 1.29)	0.21 (0.1 - 0.44)	**0.30 (0.11 - 0.78)**	0.40 (0.17 - 0.95)	1.16 (0.78 - 1.75)	1.03 (0.7 - 1.5)	G

Needed for our CEA

Modeled PFS and OS curves by treatment - constant hazard ratios



Network meta-analysis – time-varying hazard ratios

- Weibull

$$\ln\left(h_{sa}\left(t\right)\right)=\theta_{0,sa}+\theta_{1,sa}\ln\left(t\right)$$

$$\begin{pmatrix}\theta_{0,sa}\\ \theta_{1,sa}\end{pmatrix}=\begin{pmatrix}\mu_{0,s}\\ \mu_{1,s}\end{pmatrix}+\begin{pmatrix}\delta_{0,sa}\\ d_{1,1k_{sa}}-d_{1,1k_{s1}}\end{pmatrix}$$

$$\delta_{0,sa}\sim Normal\left(d_{0,1k_{sa}}-d_{0,1k_{s1}},\tau^2\right)$$

- Fractional polynomial

$$\ln\left(h_{sa}\left(t\right)\right)=\begin{cases}\theta_{0,sa}+\theta_{1,sa}t^{p_1}+\theta_{2,sa}t^{p_2} & p_1\neq p_2\\ \theta_{0,sa}+\theta_{1,sa}t^{p}+\theta_{2,sa}t^{p}\ln\left(t\right) & p=p_1=p_2\end{cases}\qquad with\ t^0=\ln\left(t\right)$$

$$\begin{pmatrix}\theta_{0,sa}\\ \theta_{1,sa}\\ \theta_{2,sa}\end{pmatrix}=\begin{pmatrix}\mu_{0,s}\\ \mu_{1,s}\\ \mu_{2,s}\end{pmatrix}+\begin{pmatrix}\delta_{0,sa}\\ d_{1,1k_{sa}}-d_{1,1k_{s1}}\\ d_{2,1k_{sa}}-d_{2,1k_{s1}}\end{pmatrix}$$

$$\delta_{0,sa}\sim Normal\left(d_{0,1k_{sa}}-d_{0,1k_{s1}},\tau^2\right)$$

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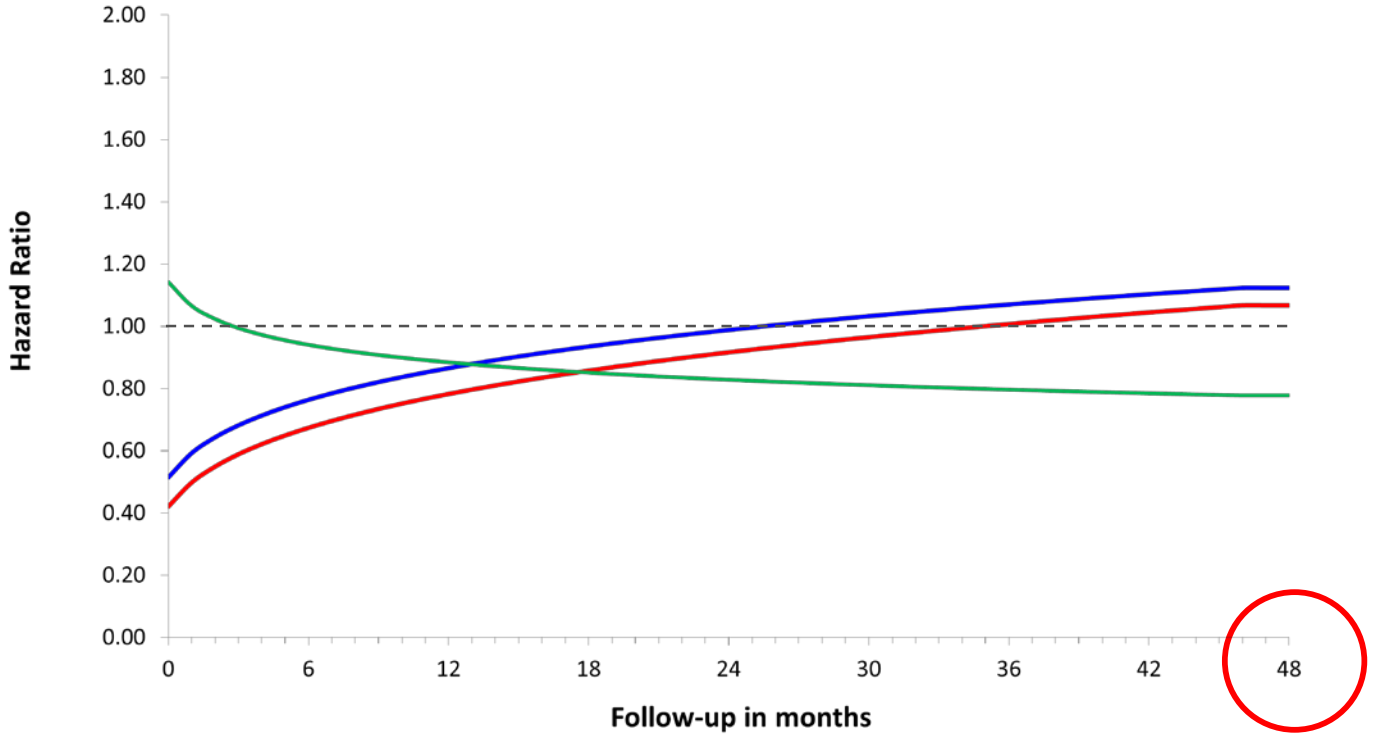
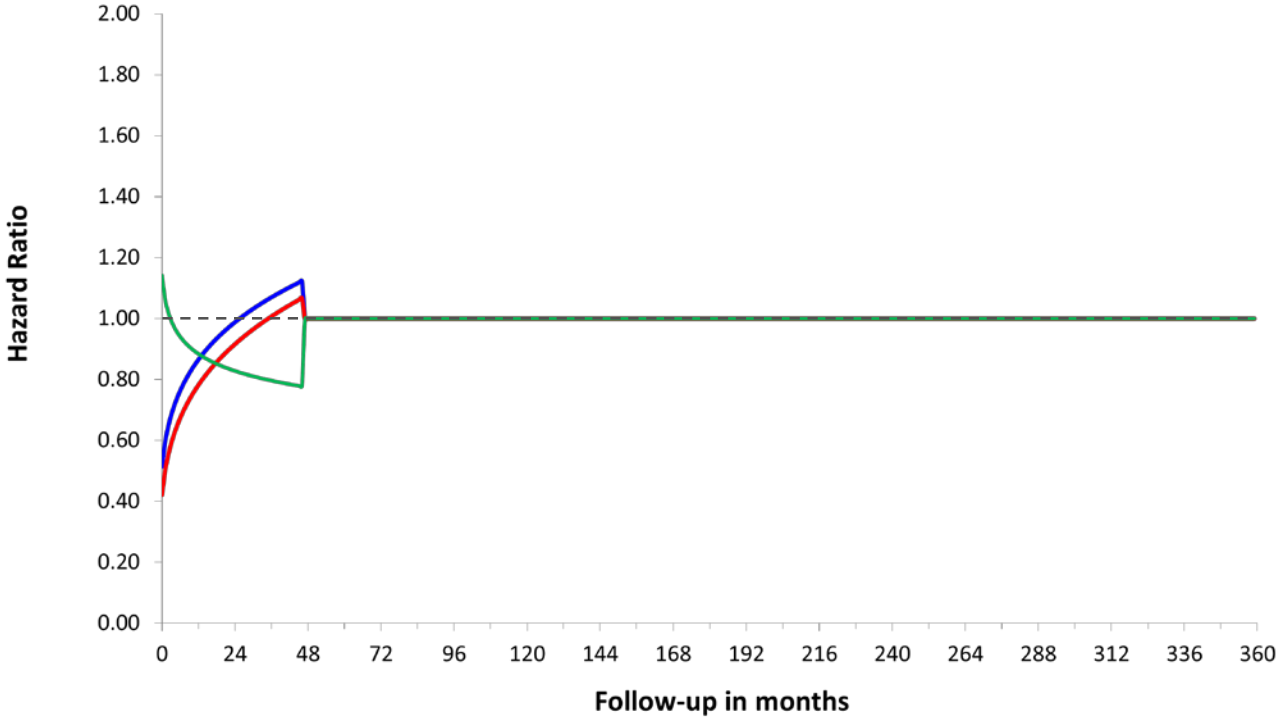


Extrapolation of relative treatment effects



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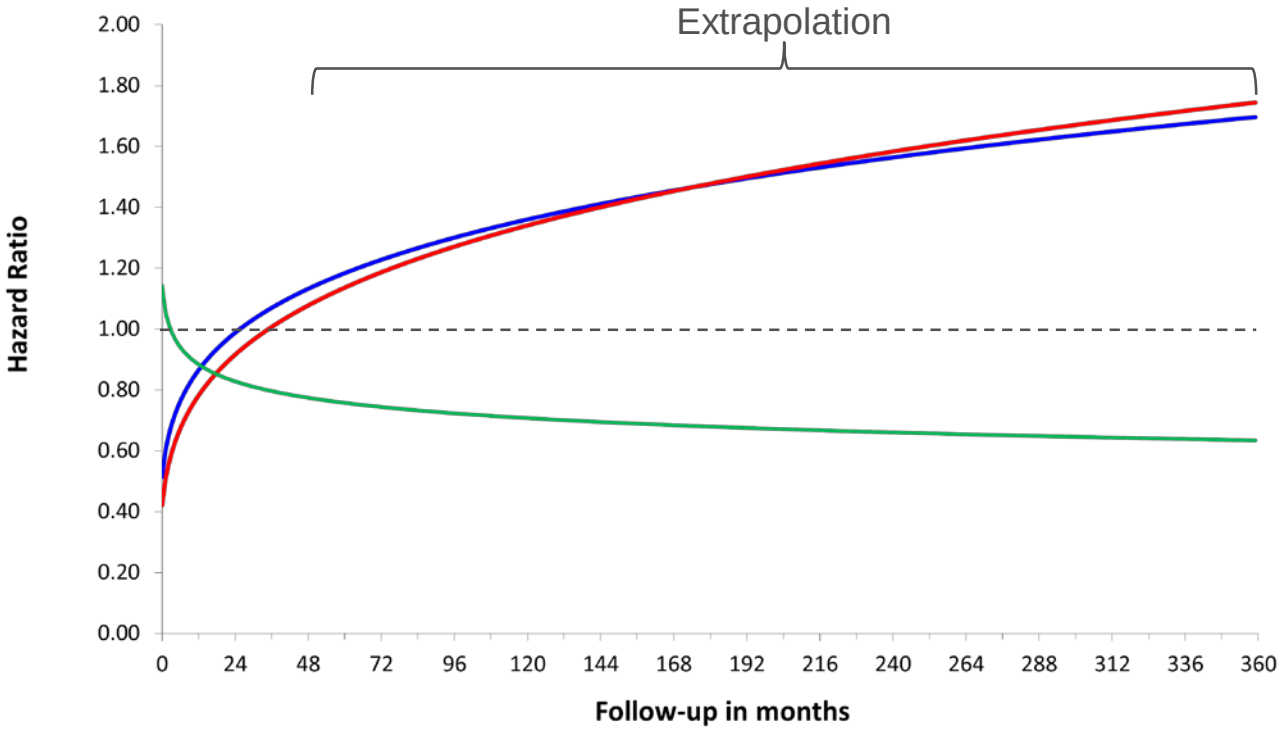

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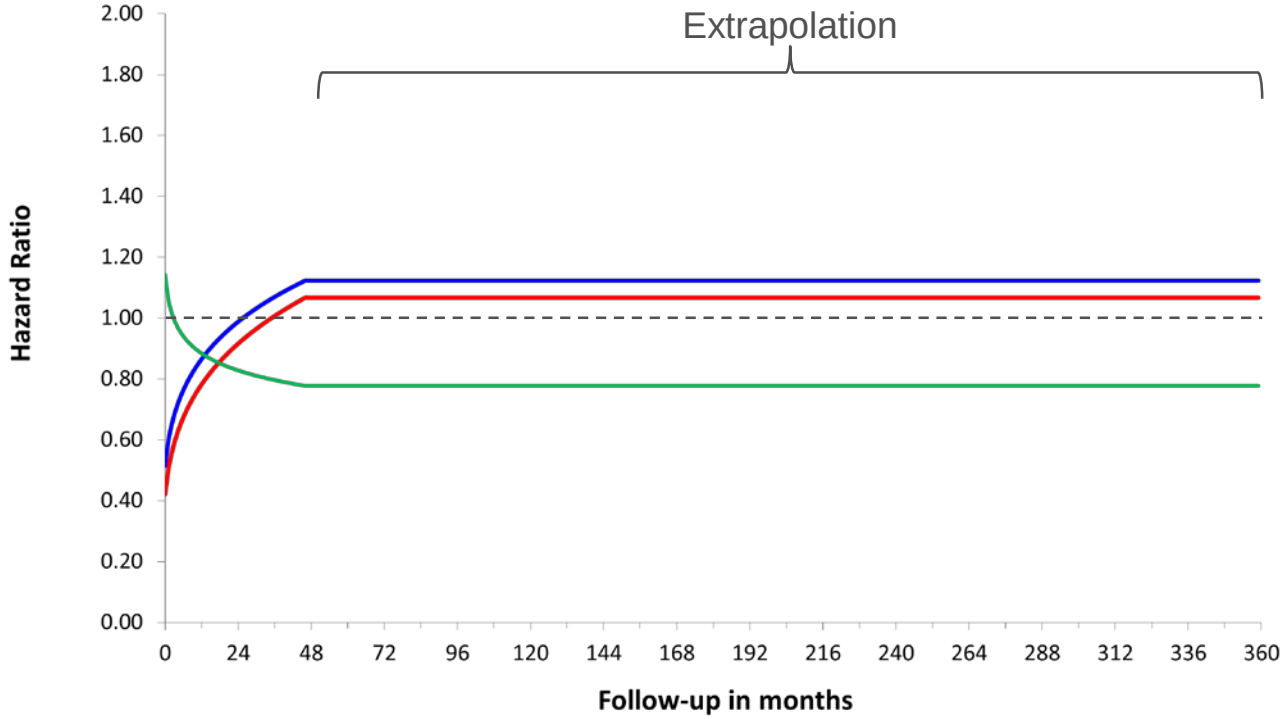
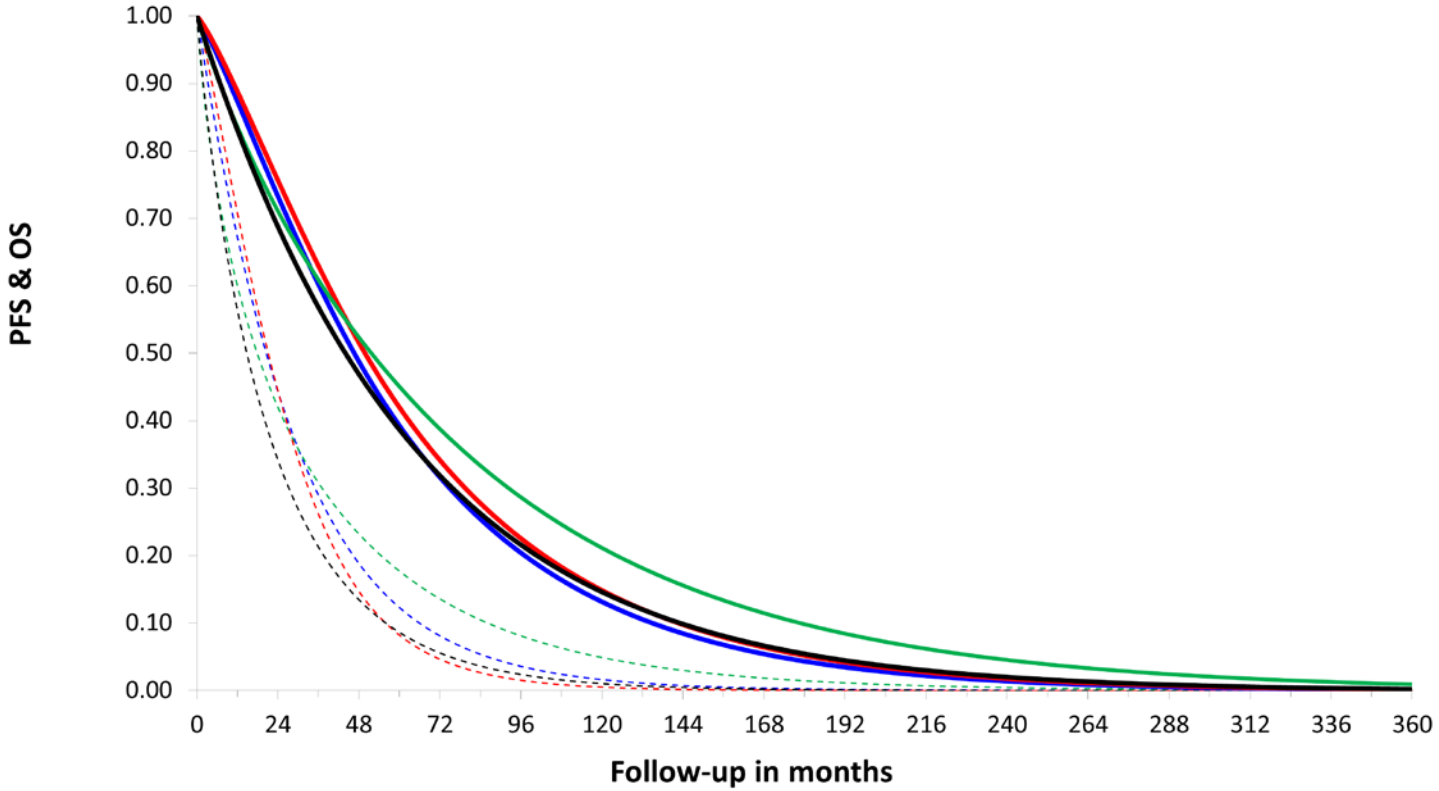


Modeled PFS and OS curves by treatment – time-varying hazard ratios



Key issues to consider

- Target population(s) of interest
  - Subgroups
  - Meta-regression
  - Use of IPD
- Model selection for evidence synthesis
  - Fit to the data
  - Extrapolation
  - Use of external evidence

Summary: Evidence synthesis for cost-effectiveness analysis

- It is the absolute difference between treatments that will determine the value of a treatment
- Assumption: absolute efficacy of a treatment may vary with the study population, the relative effect remains relatively stable
- Evidence synthesis
  - Baseline model: Absolute effect with “standard care” in routine practice
  - Relative treatment effects
- Need for extrapolation
  - Time-horizon
  - Population
  - Setting
  - ….

References

- Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis within cost-effectiveness analysis. In: Network meta-analysis for decision making. Chichester UK: John Wiley & Sons Ltd, 2018; p.155-178
- Jansen JP Cope S. Meta-regression models to assess heterogeneity and inconsistency in network meta-analysis of survival outcomes. BMC Medical Research Methodology 2012;12:152