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January 10, 2019

Advanced Methods in Bayesian Network Meta-Analysis: Recent Developments

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Data Analytics and Design Strategy
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The power of **knowledge.**
The value of **understanding.**

Presenters

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Agenda

- What is network meta-analysis?
- Development of Bayesian network meta-analysis methods
- Recent developments in Bayesian NMAs
- Case study – Survival NMA
- Conclusion

What Is NMA?

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A systematic method for pooling the evidence from independent sources

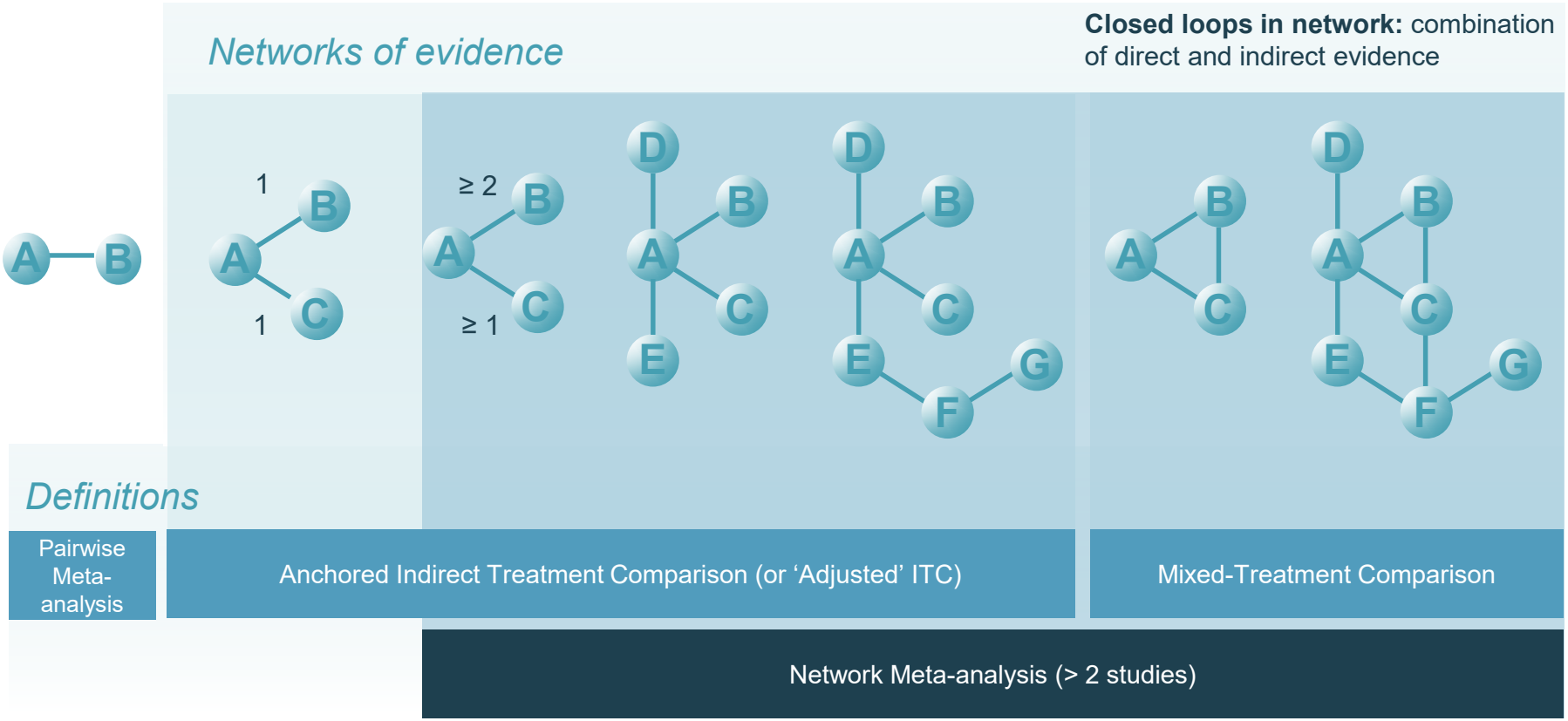

Figure adapted from:
https://www.ispor.org/workpaper/interpreting-indirect-treatment-comparison-and-network-meta-analysis-studies-for-decision-making.pdf

Development of Bayesian Network Meta-analysis

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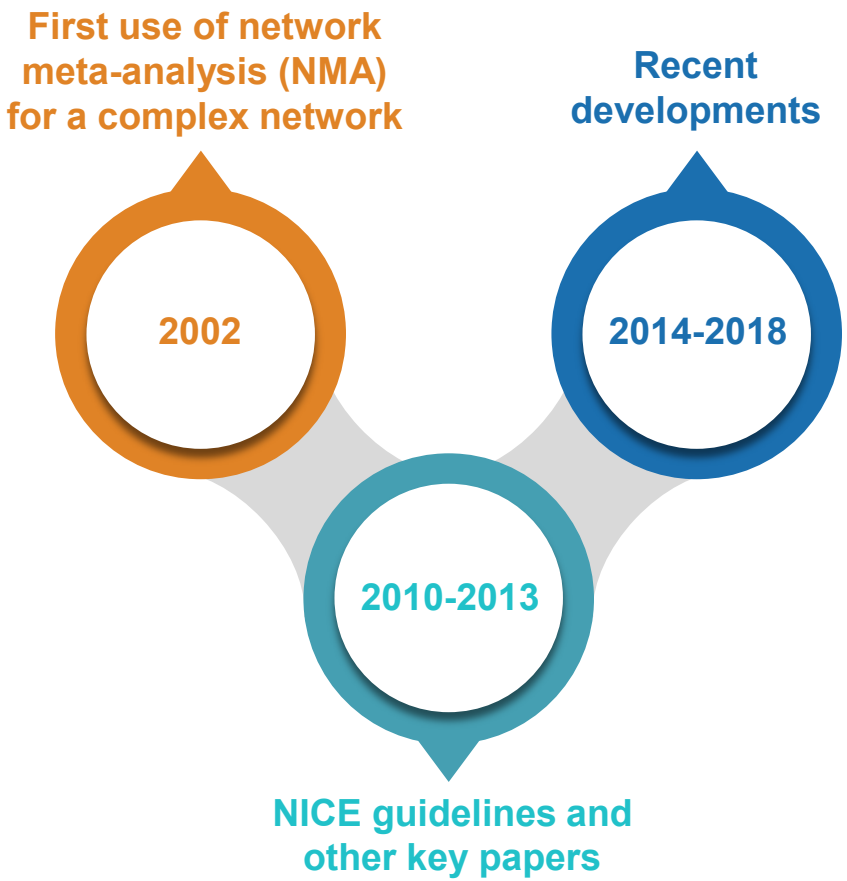


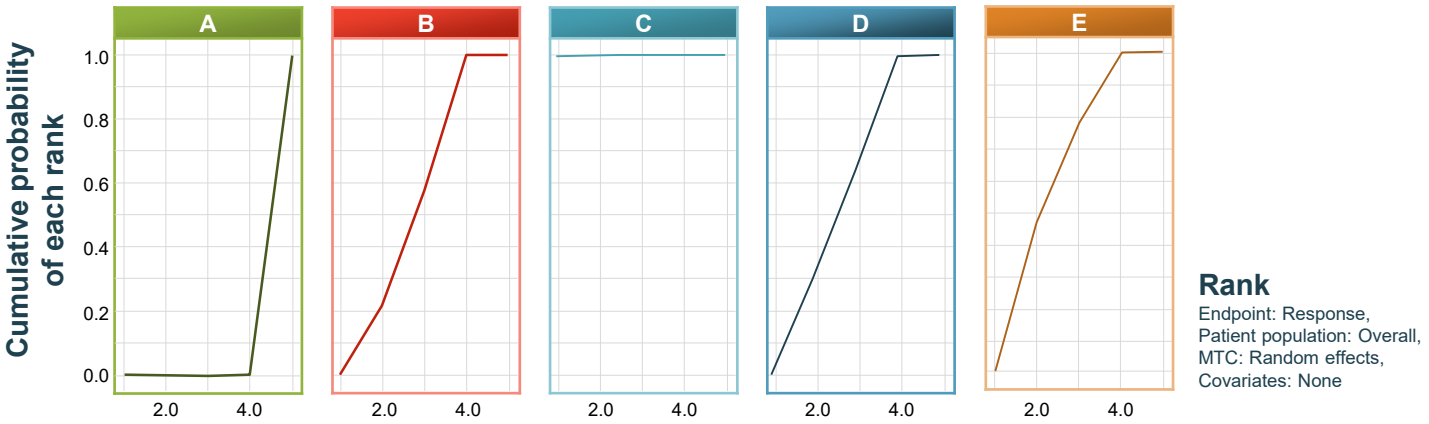
Recent developments

- Bias in the way results are presented
- Informative priors and heterogeneity
- Inclusion of real-world data
- Multivariate NMA
- Unanchored networks
- Population-adjusted NMA
- Survival analysis and NMA
- Hierarchical exchangeable models

Bias in the Way Results Are Presented

- Rankograms have been recommended as a way to consider which treatment is best
- Recent research has shown that systematic bias exists in these new methods

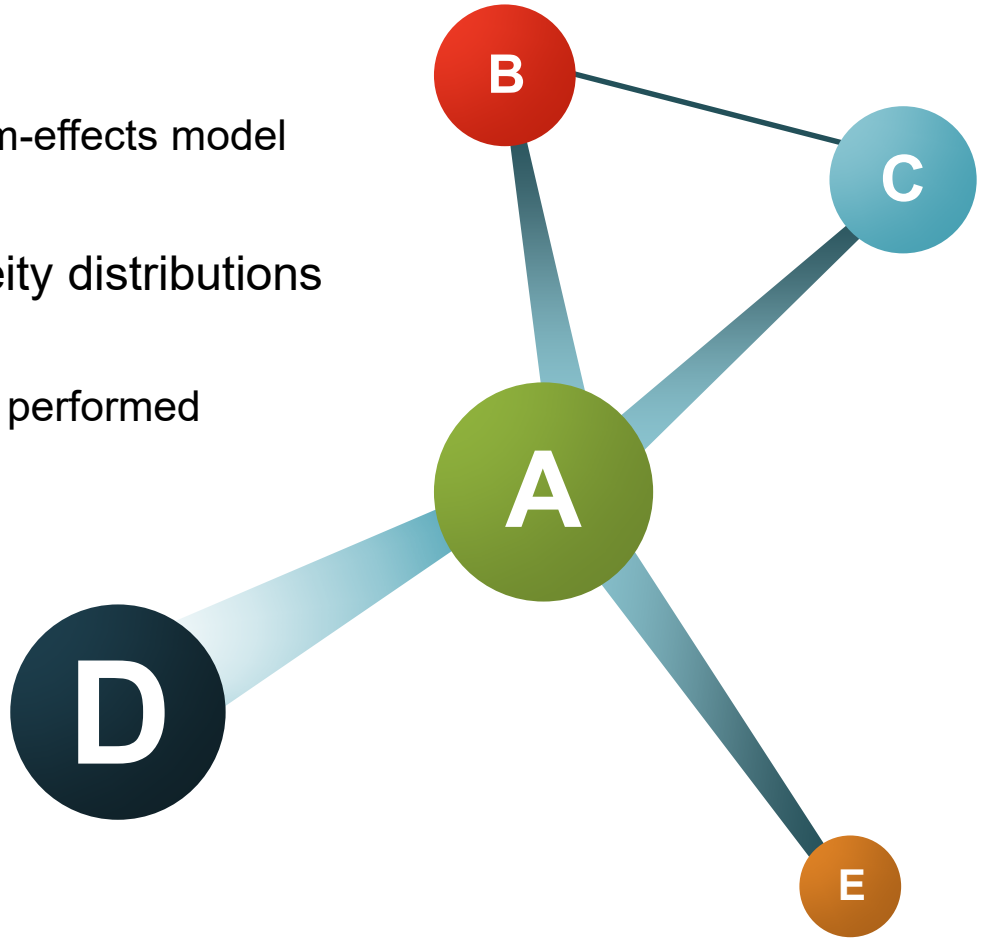
Cumulative rankograms for treatment regimens from Bayesian MTC



Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15(58):1-9.
Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol. 2011;64:163-71.

Informative Priors and Heterogeneity

- Networks are often too small
  - Heterogeneity parameter in a random-effects model difficult to estimate
- Published summaries of heterogeneity distributions used as informative priors
  - Enables random-effects NMAs to be performed



Rhodes KM, Turner RM, White IR, Jackson D, Spiegelhalter DJ, Higgins JPT. Implementing informative priors for heterogeneity in meta-analysis using meta-regression and pseudo data. Stat Med. 2016;35:5495-511.
Turner RM, Jackson D, Wei Y, Thompson SG, Higgins J. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015;34:984-98.

Inclusion of Real-World Evidence

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Problem:
NMA results from RCTs maybe inconclusive

Solution:
Include real-world evidence (RWE) in the NMA

- Three key methods to consider both RWE and RCT in NMA
- Useful to perform different models as sensitivity analyses
- Informative priors often the preferred method
- Additional uses for RWE

References:
Bell H, Wailoo AJ, Hernandez M, Grieve R, Faria R, Gibson L, et al. The use of real world data for the estimation of treatment effects in NICE decision making. 2016.
Efthimiou O, Mavridis D, Debray TPA, Samara M, Belger M, Siontis GCM, et al. Combining randomized and nonrandomized evidence in network meta-analysis. Stat Med. 2017 Apr 15;36(8):1210-1226.

Multivariate Network Meta-analysis

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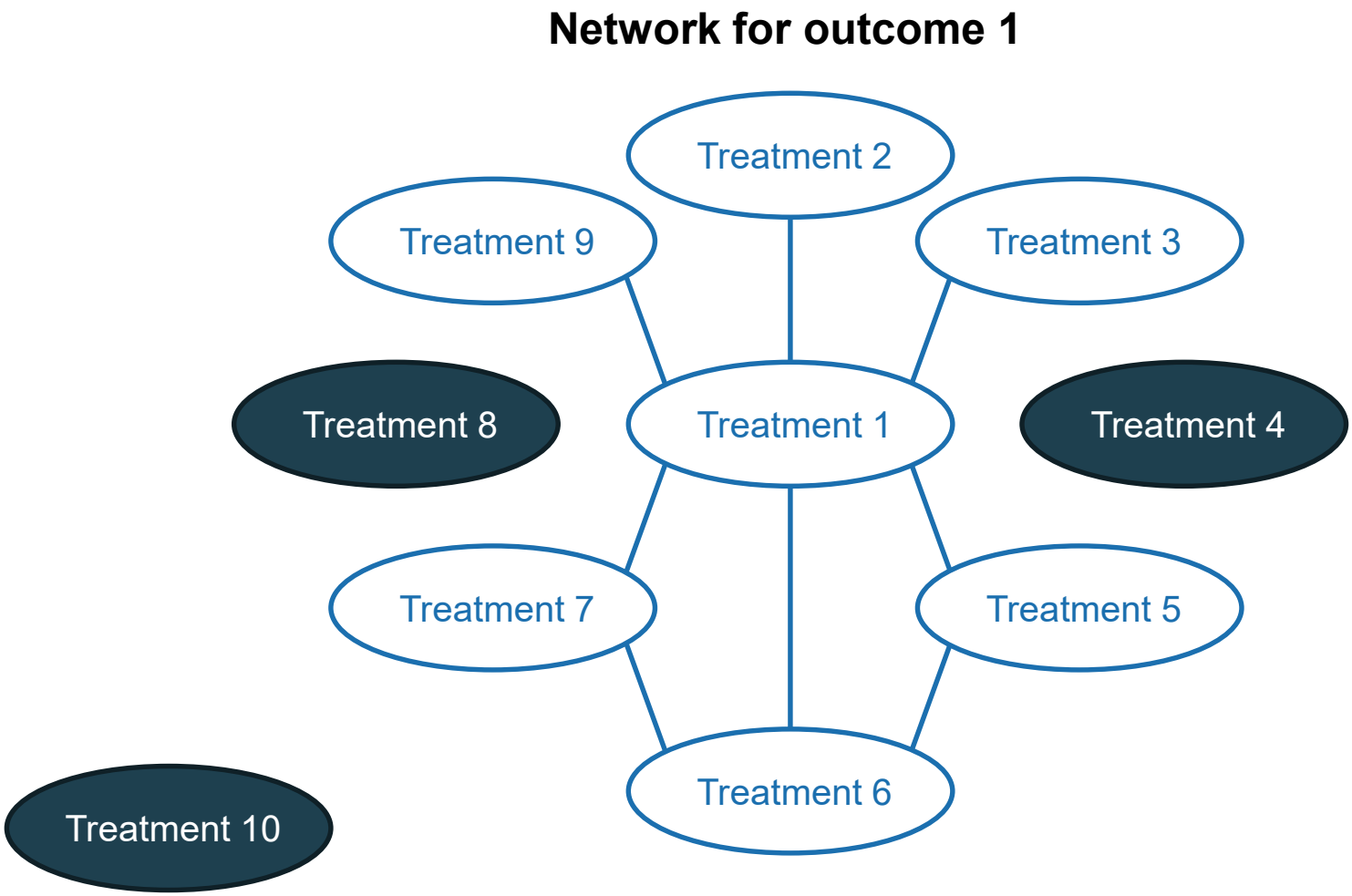

Multivariate Network Meta-analysis

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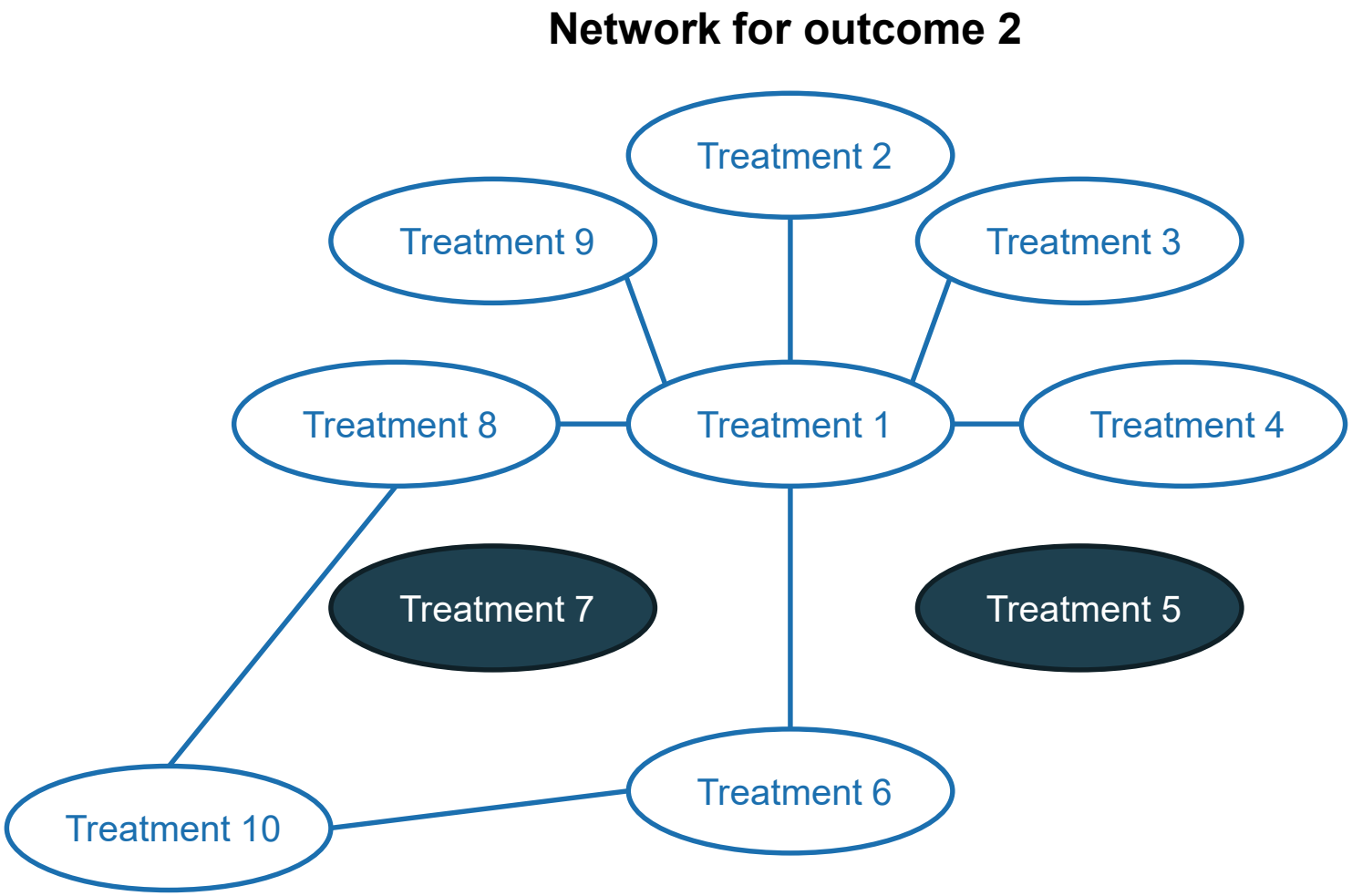

Multivariate Network Meta-analysis

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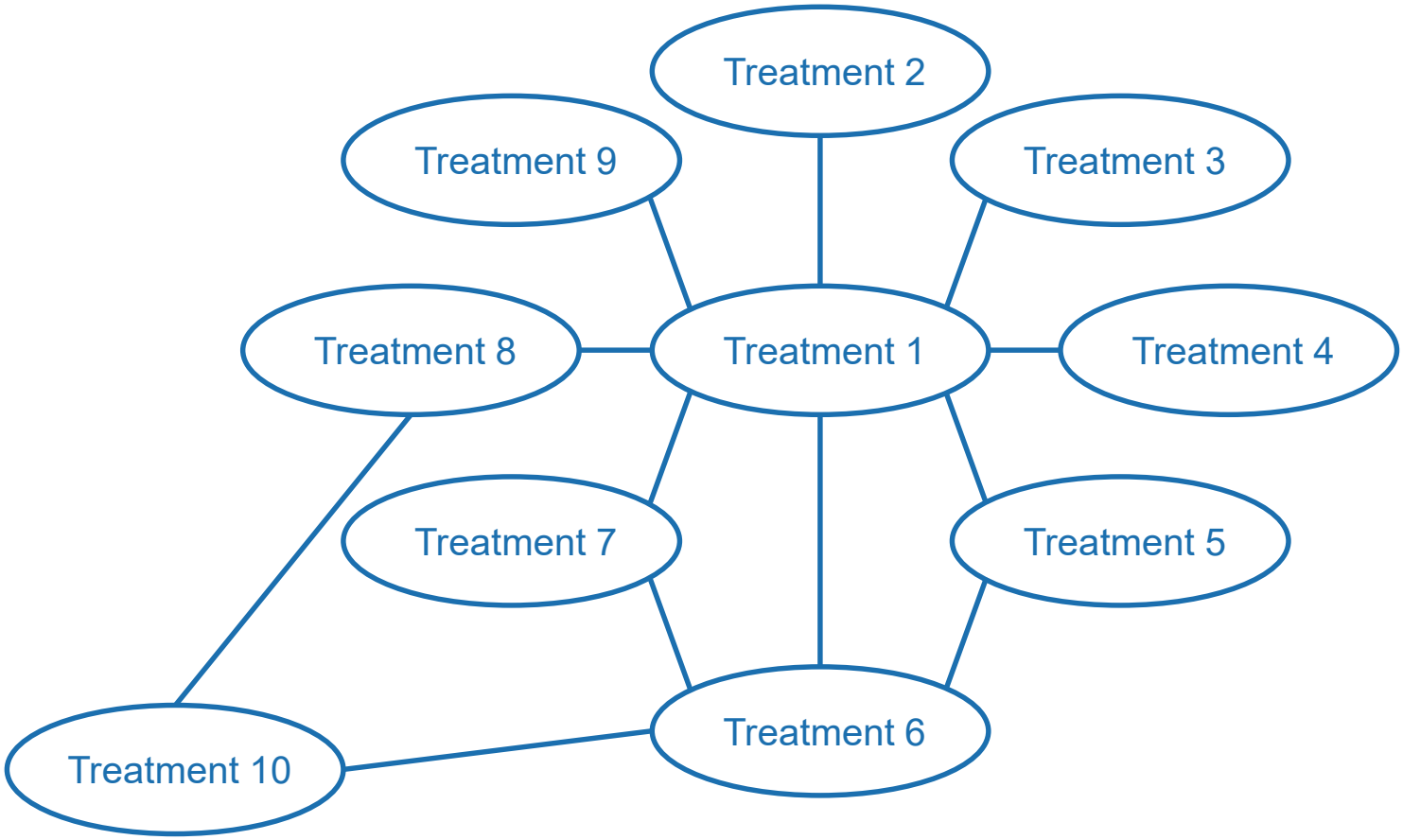
Consolidated Network for Multivariate NMA



Unanchored Networks

Problem:
We have a single arm study or no treatments are in common with other studies in the network

Solution:
Methods exist to connect a disconnected network

- However: Need individual patient-level data (IPD) in 2 studies: 1 in the network and 1 not connected to the network
  - Need overlapping patient characteristics studies
  - Assumes all important variables are included in the analysis

Reference: Faria R, Alava MH, Manca A, Wailoo AJ. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness in technology appraisal: methods for comparative individual patient data. 2015..

Population-Adjusted Indirect Comparisons

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Problem:
Patients characteristics in study with treatment of interest with IPD do not match other studies in the network.

Solution:
Match the IPD data to one of the other studies in the network.

- **Criticism**: The answer differs according to:
  - Which study contains the IPD data
  - Which study we match our study to if >1 other study in the network
- **Alternative method**: NMA that combines IPD and summary level data

Reference: Phillippo DM, Ades AE, Dias S, Palmer S, Abrams K, Welton NJ. NICE DSU Technical Support Document 18: methods for population adjusted indirect comparisons in submission to NICE. 2016

NMA and Survival Analysis

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Problem:

Traditionally NMA has relied on hazard ratios. However, non-proportional hazard ratios are commonly found in RCTs

Solution:

Models fitted to reconstructed patient-level data

- Standard parametric models
- Fractional polynomial models
- Spline-based models

Fractional polynomial models typically gives a good balance between modelling complexity and convergence.

- **Criticism**: Need to be aware of possible publication bias.

Reference for choice of model: Vickers AD. Survival network meta-analysis: Hazard ratios versus reconstructed survival data. Poster presentation at ISPOR 21st Annual International Meeting; May 21-25, 2016. Washington, DC, United States.

Hierarchical Exchangeable Models

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Problem (1):

Correlations may exist in a network:

- Treatments within a class of treatment
- Dose regimens for a single treatment
- Subgroups of patients from the same study

Problem (2):

Certain treatments interact with particular patient characteristics

Solution:

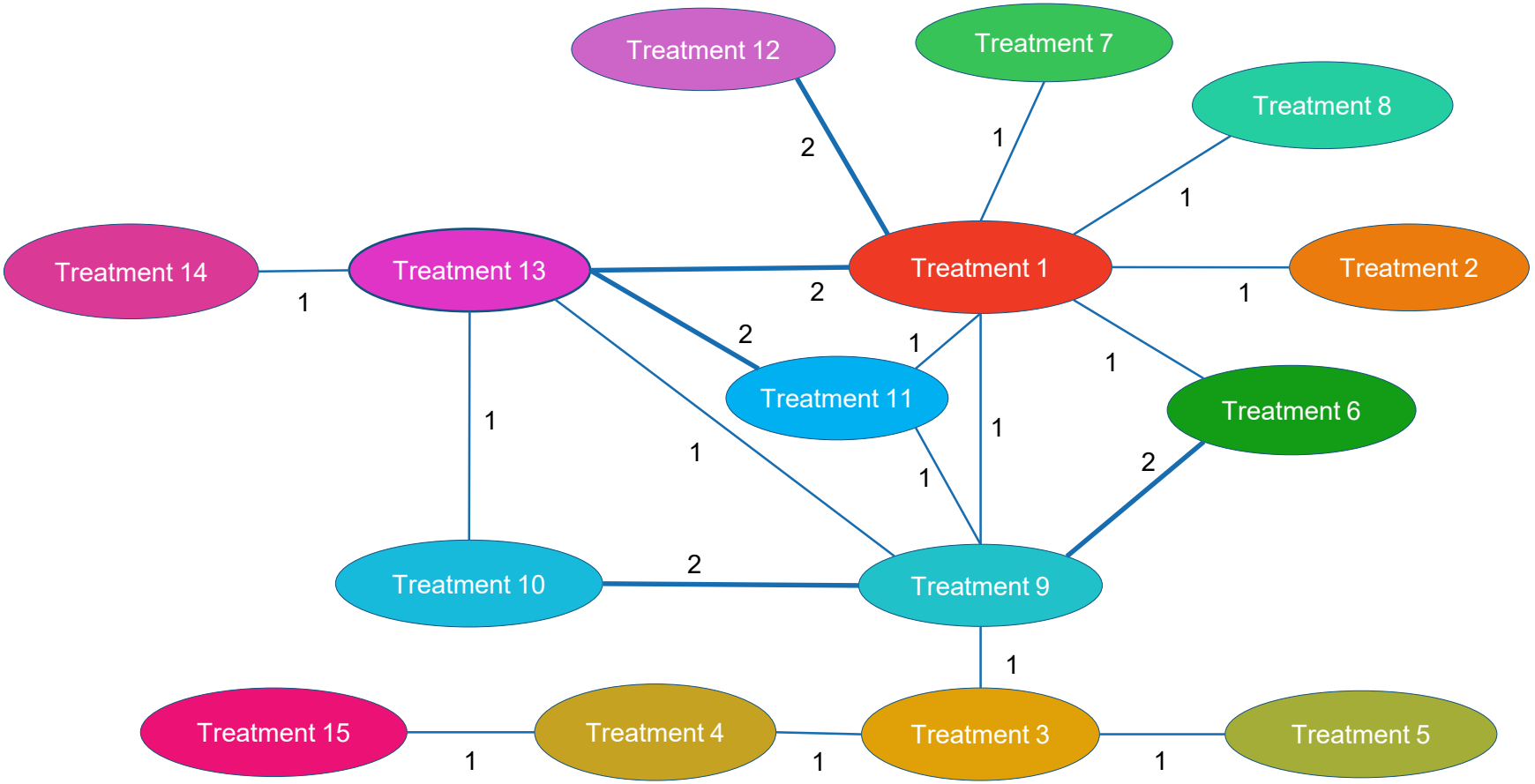
Hierarchical exchangeable model

- Need to have evidence that treatments behave differently

Reference: Owen RK, Tincello DG, Abrams K. Network meta-analysis: development of a three-level hierarchical modeling approach incorporating dose-related constraints. Value Health. 2015;18:116-26.

Case Study: The Network

Complex network, which includes duplicate comparisons and closed loops



Note: Numbers refer to the number of studies.

Case Study: a Survival Network Meta-analysis

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Problem (1):
Non-proportional hazards

Solution:
Fractional polynomial model fitted to reconstructed patient level data

Case Study: a Survival Network Meta-analysis

Problem (2):

Treatment interactions

- 2 treatment classes were designed to target particular tumor biomarkers
- 2 treatments have different effects according to tumor tissue type

Solution:

Hierarchical exchangeable model

- Allowed specific treatment effects to behave differently for the relevant subgroup
- The treatment effect for other interventions remained constant

Case Study: Survival Predictions for Each Trial Arm Plus Kaplan-Meier Estimates

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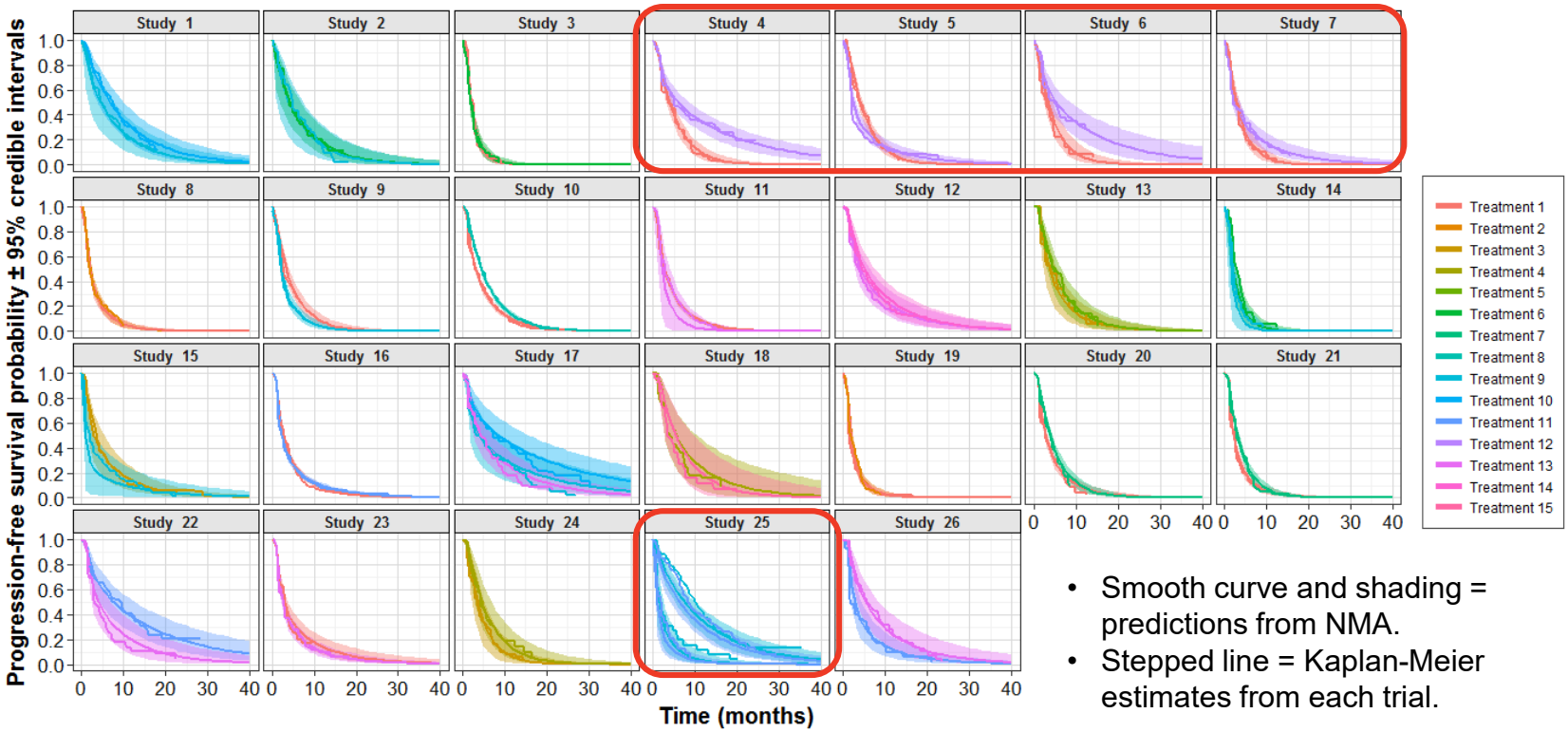
- Studies 4, 5, 6, and 7 were subgroups from the same study
  - Survival curve for Treatment 1 remained constant, but Treatment 12 varied by subgroup
- Study 25: Both treatments (9 and 11) varied by subgroup



- Smooth curve and shading = predictions from NMA.
- Stepped line = Kaplan-Meier estimates from each trial.

Case Study: Predictions Made From the Survival Network Meta-analysis

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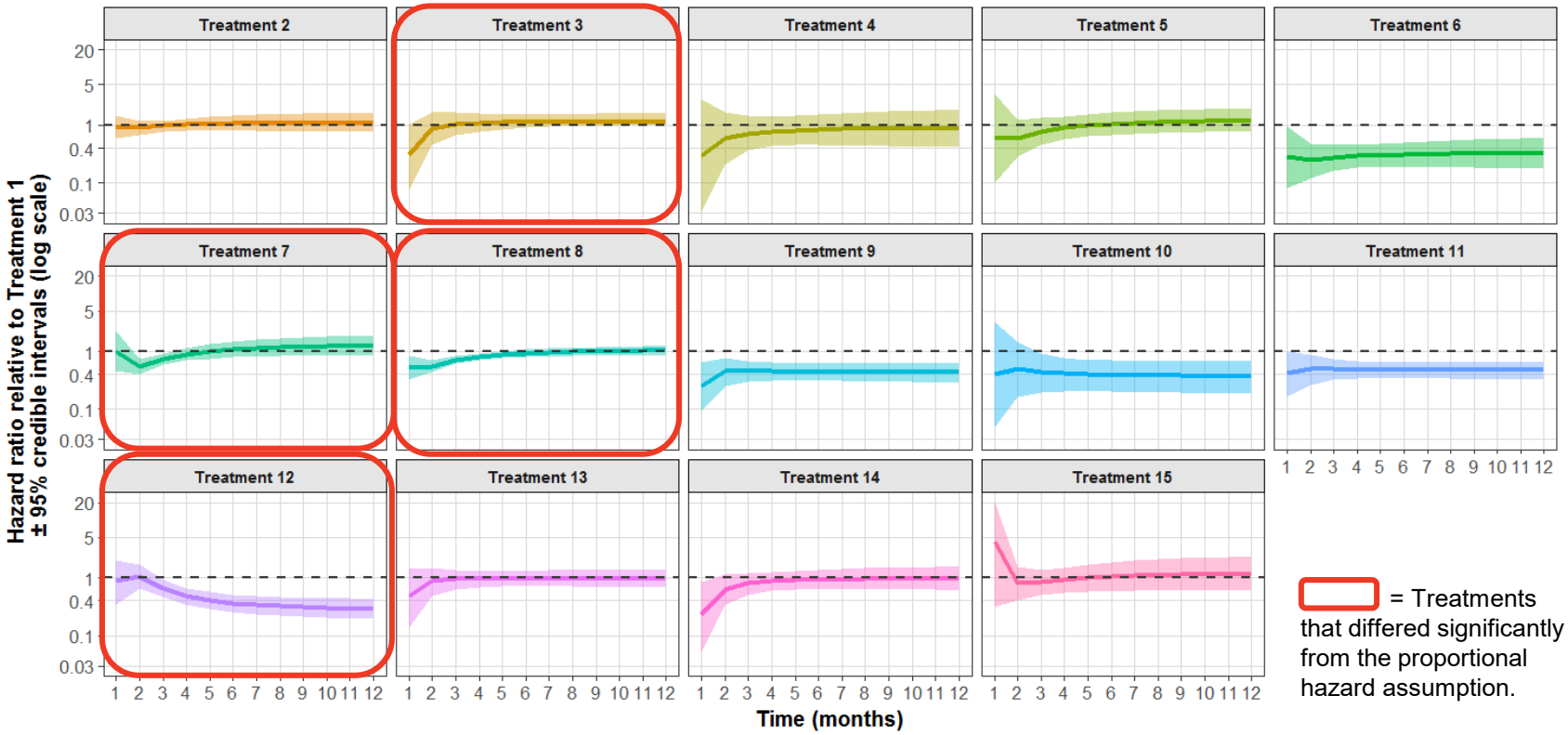
- There were 8 possible combinations of subgroups
  - Tissue types (2 categories)
  - Biomarker 1 (2 categories)
  - Biomarker 2 (2 categories)
- The next 4 slides presents 1 of the 8 subgroups.
- This piece of work has recently been submitted for publication and the results for all 8 subgroups are presented

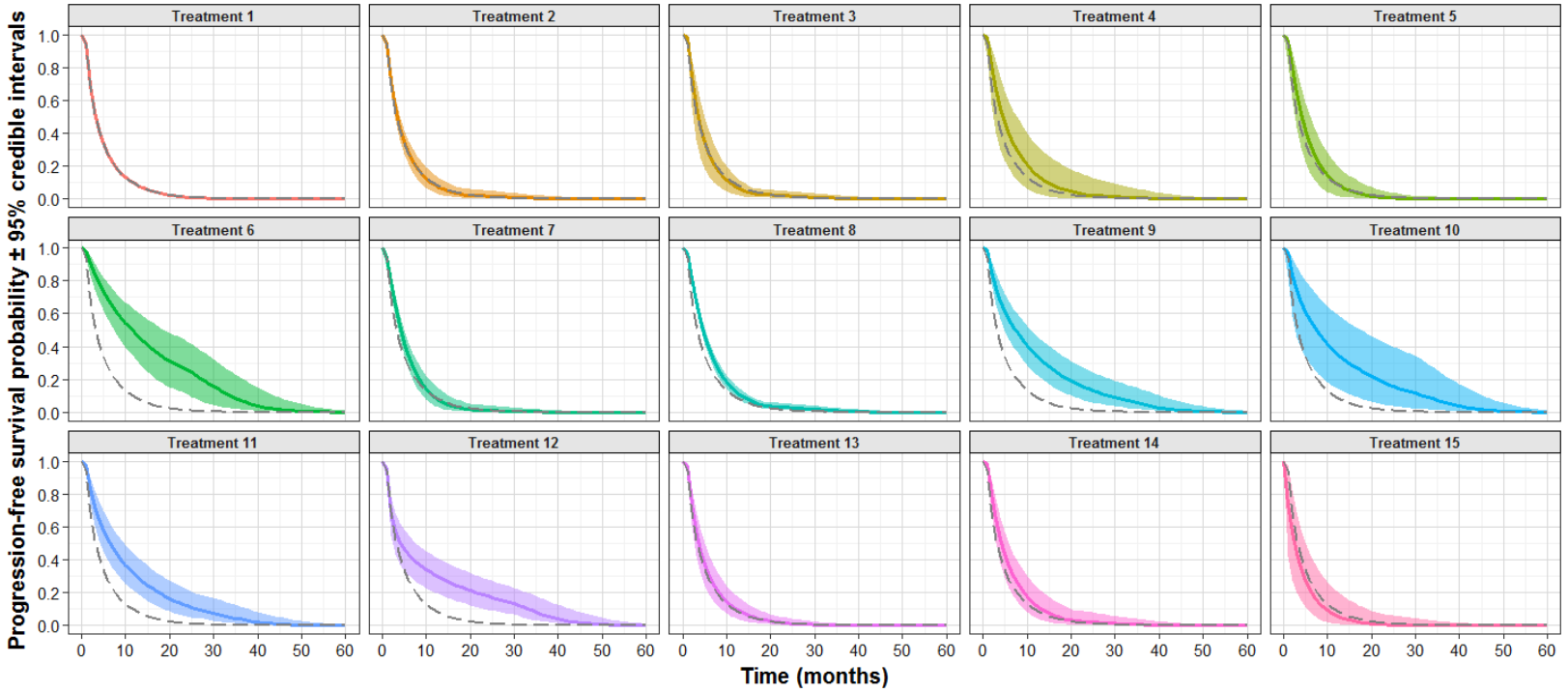
Case Study: Hazard Ratios Over Time

- Hazard ratios for some treatments change over time
- A flat horizontal line indicates the proportional hazard assumption had been met



Case Study: Predicted Survival Curves

- Extrapolation:
- After the maximum follow-up time for each treatment had been reached, the hazard rates from the reference treatment were used.



Case Study: Predicted Mean Survival Times

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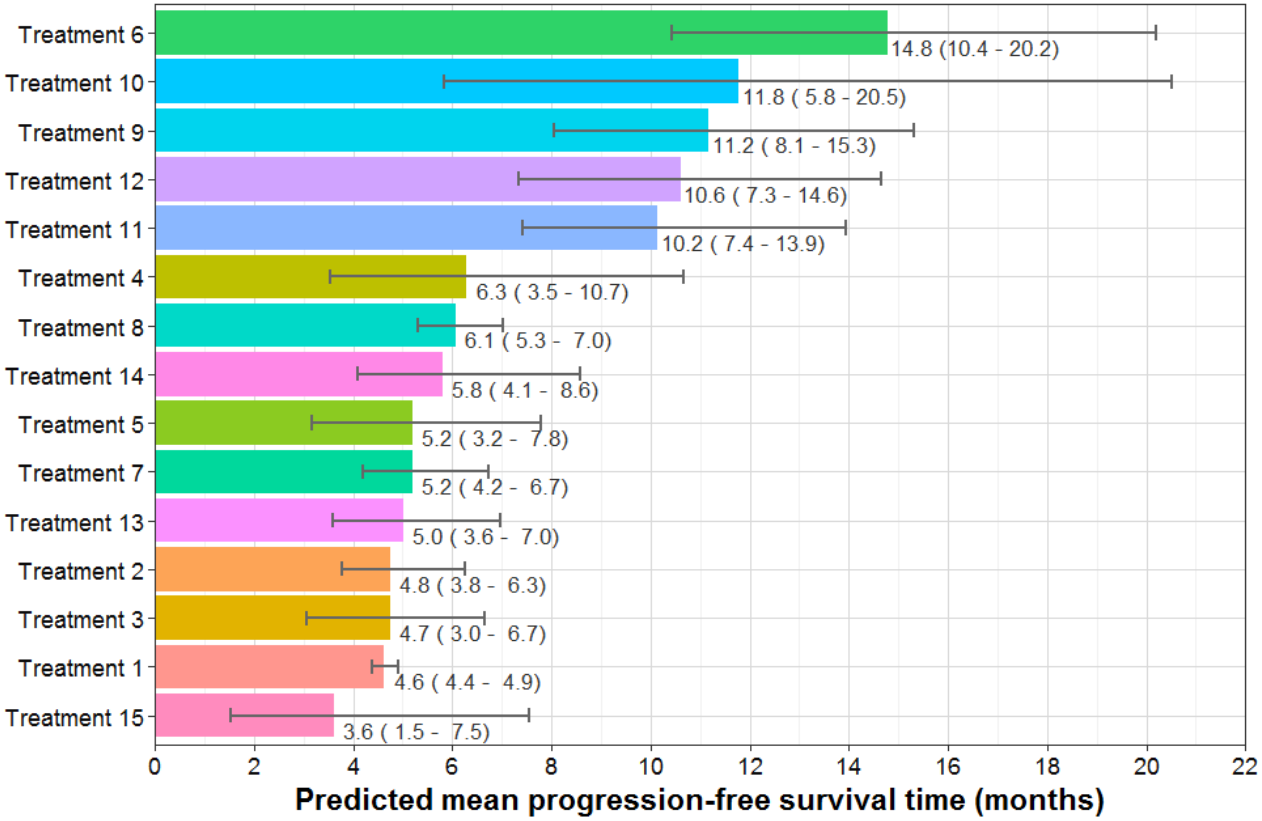
- Predicted mean progression-free survival (area under survival curve)



Case Study: All Pairwise Differences: Mean Survival Times

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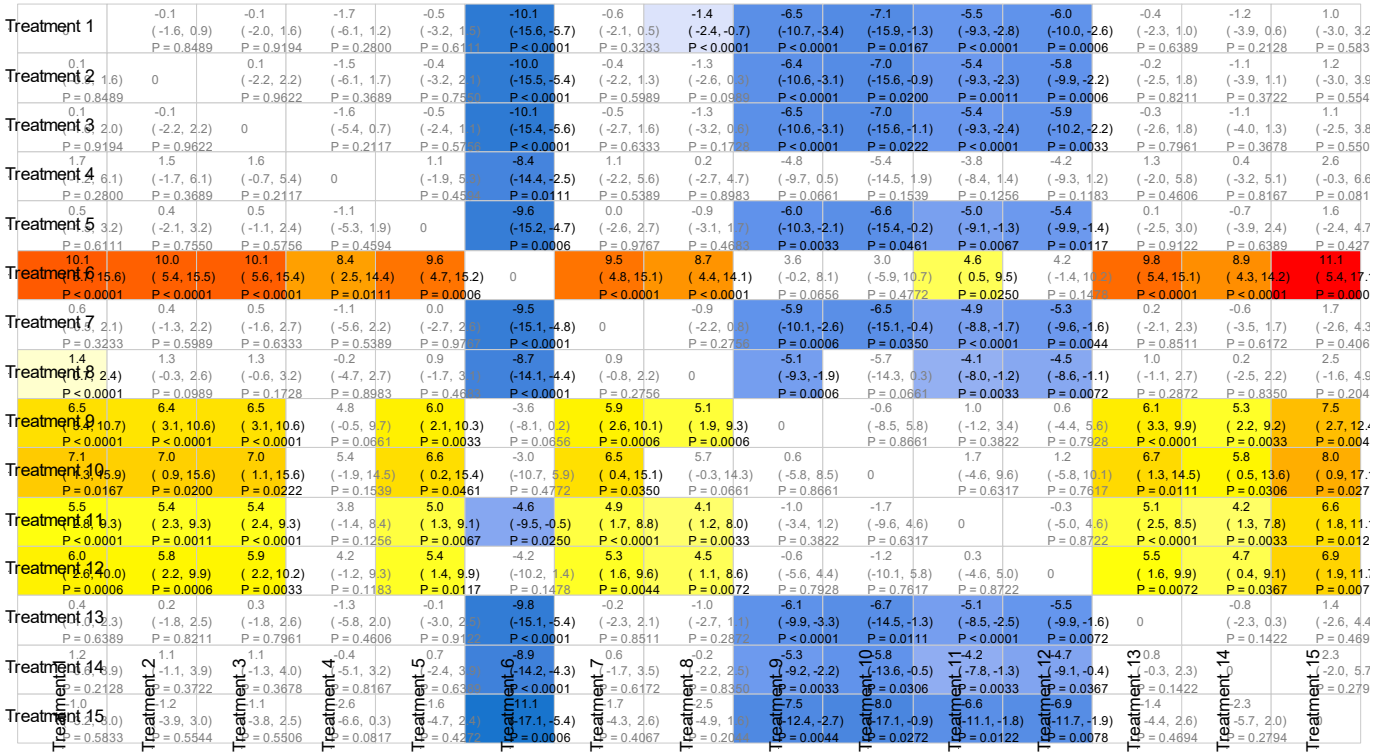
- Yellow to red = treatment on a horizonal line significantly better than on the vertical line.
- Blue = treatment on a horizonal line significantly worse than on the vertical line.



NMA and Health Technology Assessments

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- Most countries now follow the UK NICE guidelines
- NICE DSU documents are relatively slow to keep up with the literature; currently no guidelines for:
  - NMAs based on survival data
  - NMA regression models that combine IPD and summary data
  - Multivariate NMA: model 2 or more correlated endpoints simultaneously
  - Use of informative priors for random-effects models
- The main pressure for a particular model typically comes from comments from the economic research group (ERG) used to advise NICE on the appropriateness of the method presented

Conclusion

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- NMA methods are continuing to develop at a rapid rate
- Many methods have not been thoroughly tested, so methods are still changing as simulation studies are conducted
- For a given problem, there may be several possible methods
- Important to make sure the following are met
  - Transparent
  - Low risk of bias
  - Assumptions in the model have been met and are clearly stated
  - Heterogeneity and inconsistency have been explored
  - Sensitivity analyses conducted where needed

Thank You
Questions?

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