At first I was afraid, I was petrified...

Issues and Possible Solutions to Extrapolating Survival Curves from Limited Trial Data

Spotlight session, ISPOR EUROPE

2nd December, 2021

Moderator: Zhaojing Che

Panelists: Gianluca Baio, Victoria Paly

Today's speakers

Victoria Federico Paly, MHS

Senior Principal

ICON plc

Gianluca Baio, PhD

Professor

University College London

Zhaojing Che, MSc

PhD student

University College London

Blended Survival Curves: A New Approach to Extrapolation from Limited Trial Data

Zhaojing Che

(Joint work with Gianluca Baio and Nathan Green)

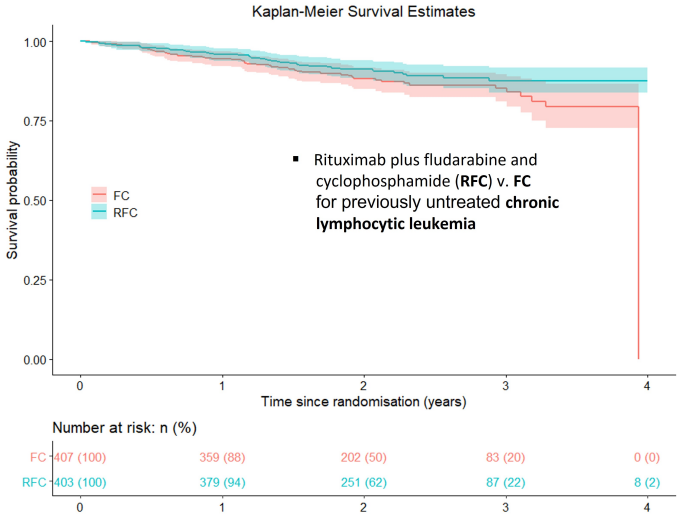
December, 2021

Department of Statistical Science, University College London

Survival modelling in HTA

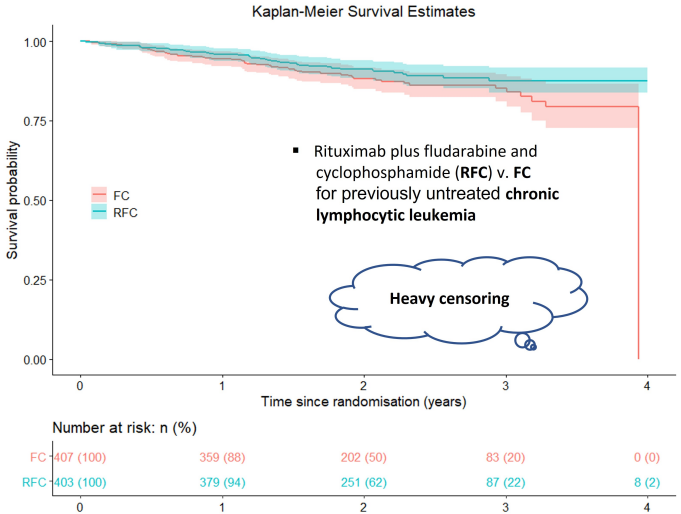
- Development of innovative (anti-cancer) drugs
  - Clinical delayed effects
  - Possible long term survivors
- Problem: **Heavy Censoring** due to limited follow-up
- **Objective**: provide credible estimate of survival extrapolation
  - new method: “blending” survival curves
- Example: CLL-8 Trial data

Limited RCT data



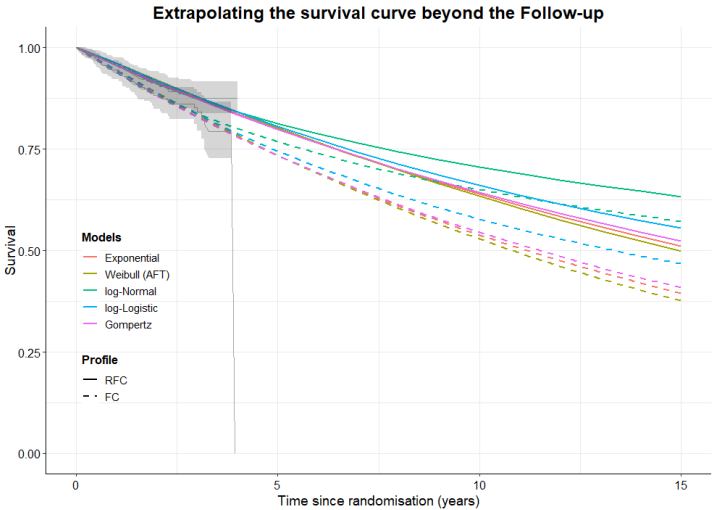
National Institute for Health and Clinical Excellence. Rituximab for the first line treatment of chronic lymphocytic leukaemia. Available from: http://guidance.nice.org.uk/TA174

Limited RCT data

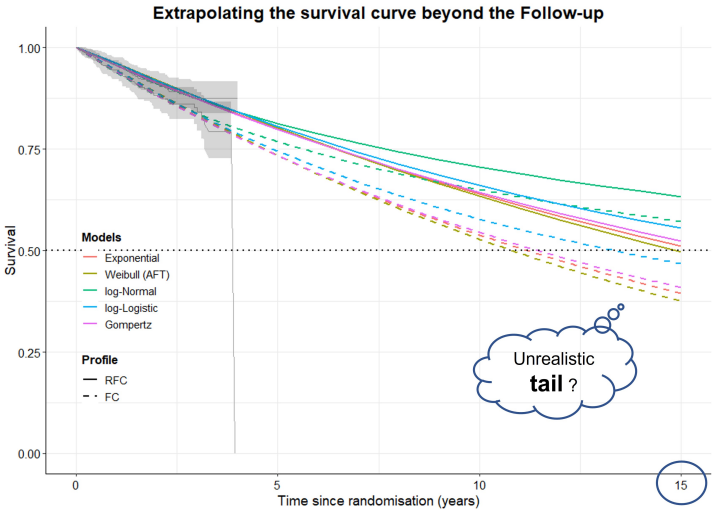


National Institute for Health and Clinical Excellence. Rituximab for the first line treatment of chronic lymphocytic leukaemia. Available from: http://guidance.nice.org.uk/TA174

Extrapolation: parametric models?



Extrapolation: parametric models?



Long-term behaviour

Using **external information**:

- External data: registries, cancer cohort
  - Long-term dataset

Long-term behaviour

Using **external information**:

- External data: registries, cancer cohort
  - Long-term dataset
- Elicited beliefs: expert opinion/knowledge
  - 5/10-y survival probability
  - Mortality for disease-related causes...

Long-term behaviour

Using **external information**:

- External data: registries, cancer cohort
  - Long-term dataset
- Elicited beliefs: expert opinion/knowledge
  - 5/10-y survival probability
  - Mortality for disease-related causes...

At 10 years what is the plausible range of survival probabilities for Treatment X?

Long-term behaviour

Using **external information**:

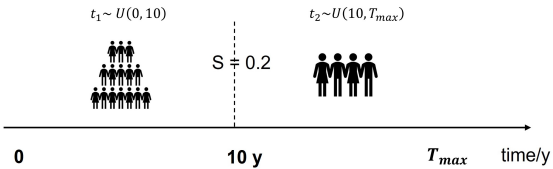
- External data: registries, cancer cohort
  - Long-term dataset
- Elicited beliefs: expert opinion/knowledge
  - 5/10-y survival probability
  - Mortality for disease-related causes...

At 10 years what is the plausible range of survival probabilities for Treatment X?

We consider a parametric model encoding assumptions on the expected long-term behaviour.

Incorporating external information

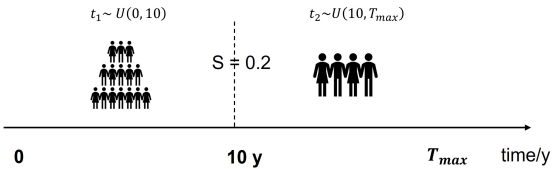
Artificial data set:



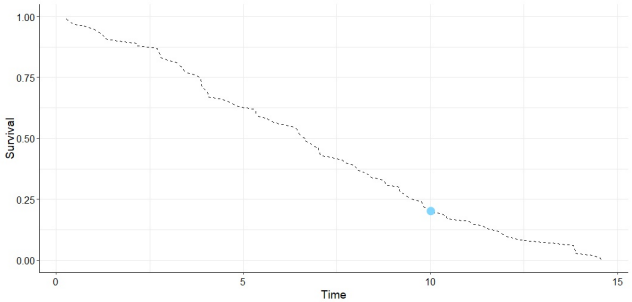
Clinician opinion:
"At 10 years, the most likely survival probability is around 0.2"

Incorporating external information

Artificial data set:

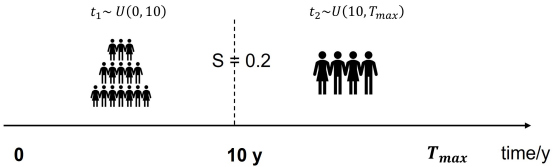


Clinician opinion:
"At 10 years, the most likely survival probability is around 0.2"

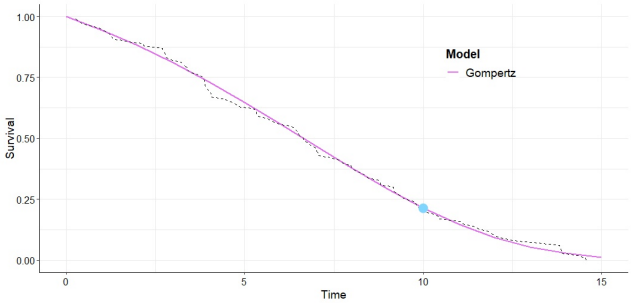


Incorporating external information

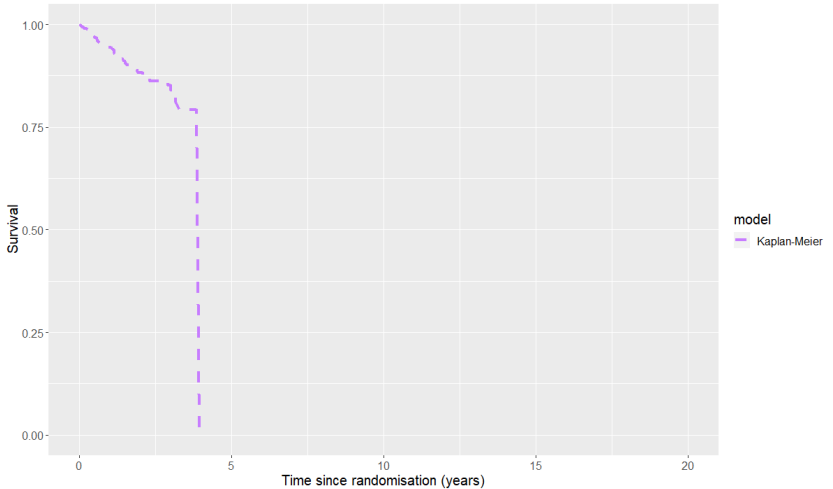
Artificial data set:



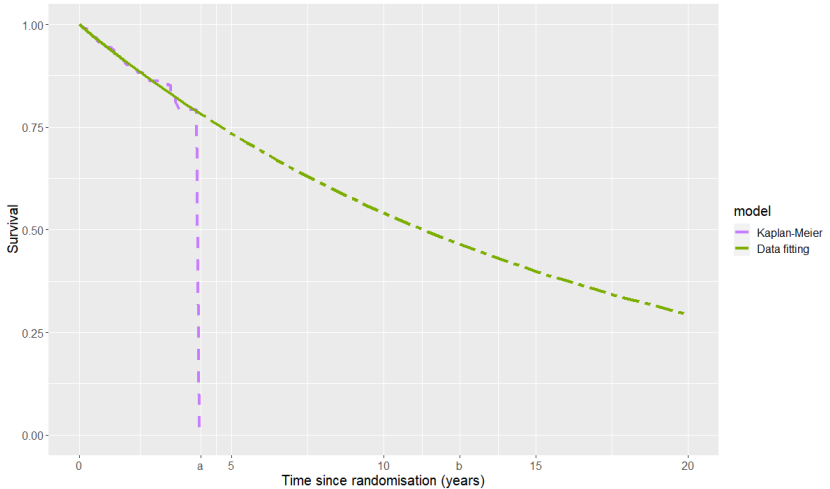
Clinician opinion:
"At 10 years, the most likely survival probability is around 0.2"



Observed data

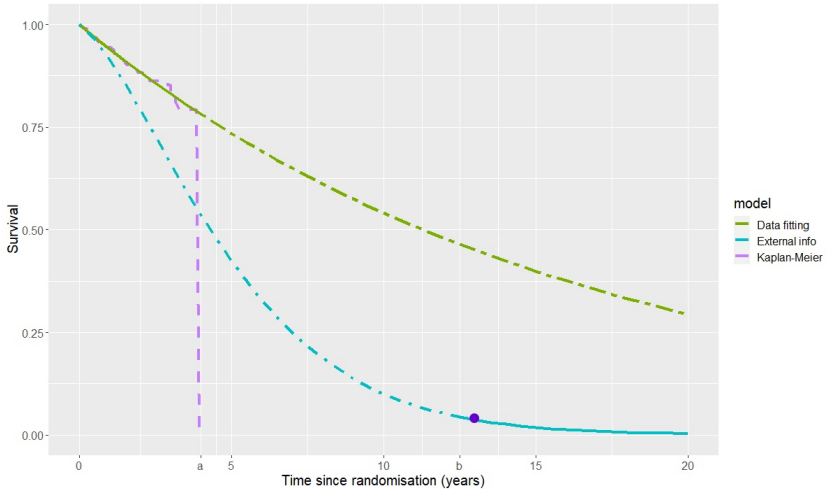


Observed data

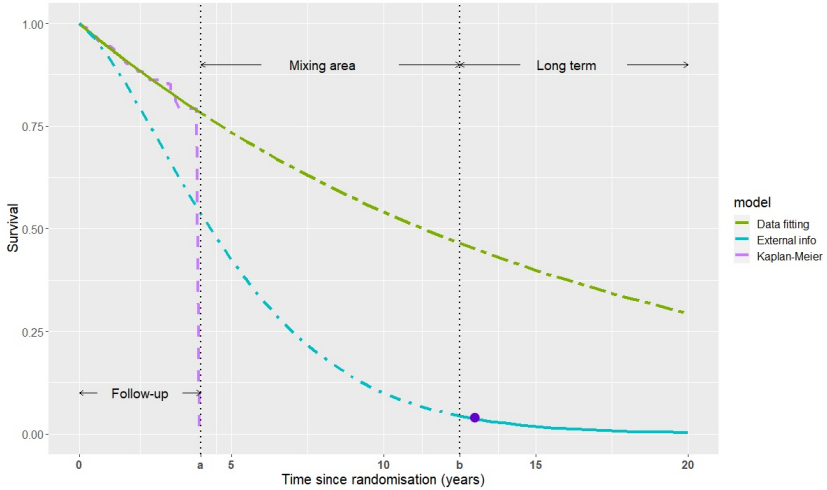


Martino, S., Akerkar, R., Rue, H. (2011). Approximate Bayesian Inference for Survival Models. Scandinavian Journal of Statistics, 38(3), 514–528

Blended curves

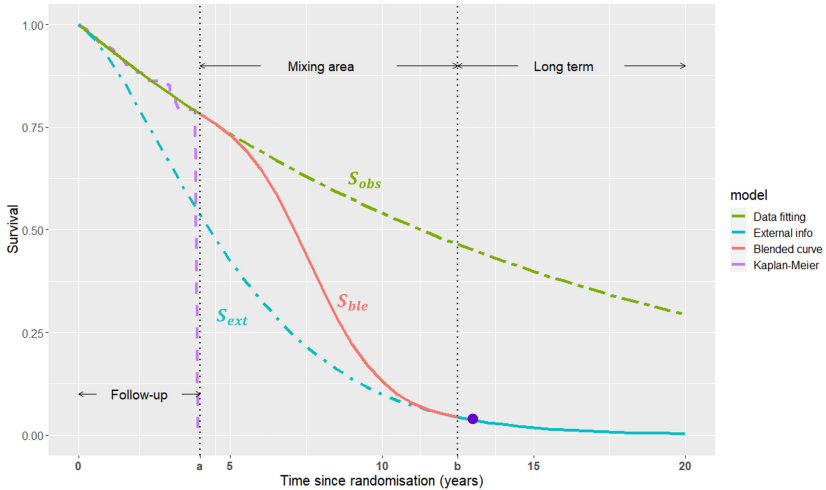


Blended curves



Blended curves

$$\log S_{ble} = (1 - p) \cdot \log S_{obs} + p \cdot \log S_{ext}$$

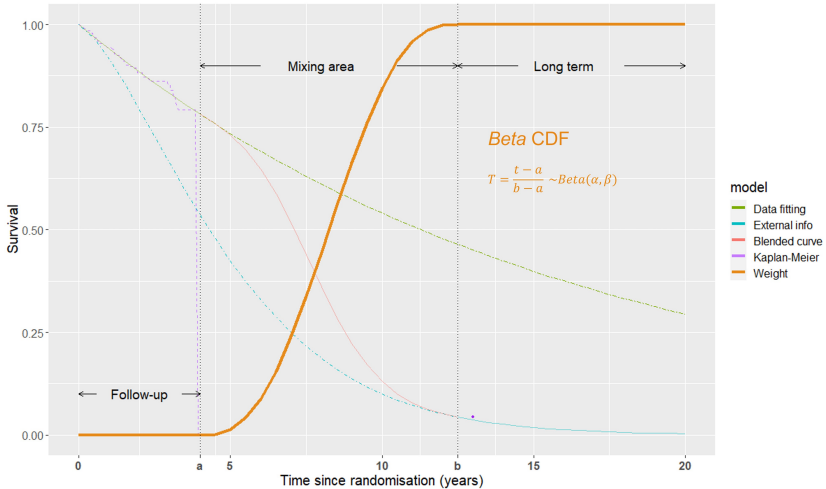


Castro-Camilo, D., Huser, R. and Rue, H., 2021. Practical strategies for GEV-based regression models for extremes.

Weight function

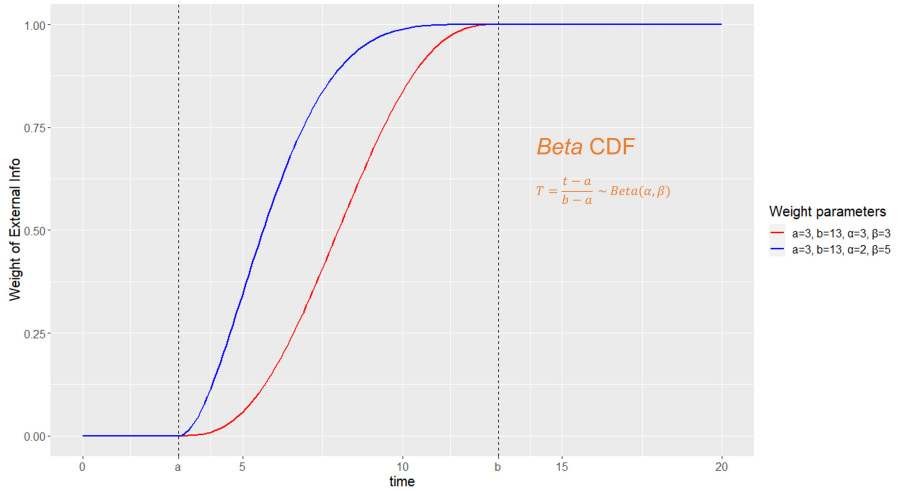
$$\log S_{ble} = (1 - p) \cdot \log S_{obs} + p \cdot \log S_{ext}$$

$$p = \Pr(T \leq \frac{t-a}{b-a} | \alpha, \beta)$$

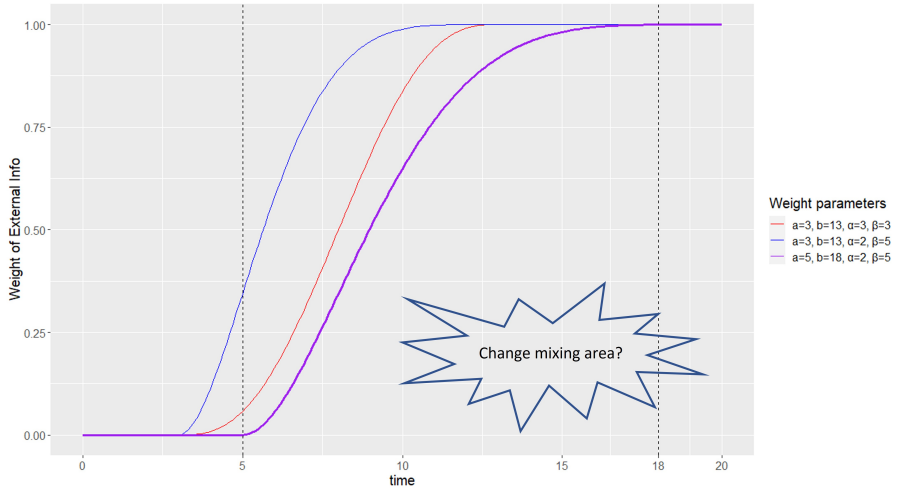


Castro-Camilo, D., Huser, R. and Rue, H., 2021. Practical strategies for GEV-based regression models for extremes.

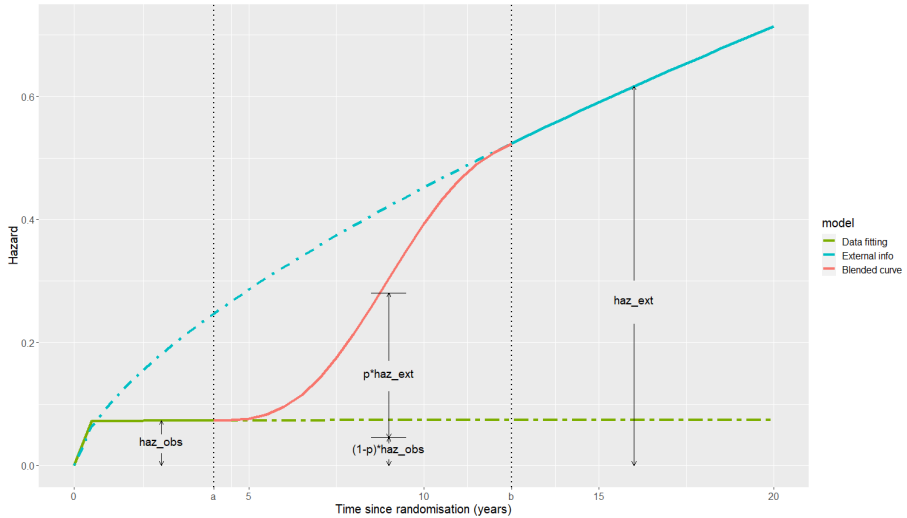
Weight function



Weight function



Blended hazards?



So this is like mixture cure model?...

Actually, no...

- Mixture Cure Model
  - considers two components (“cured” vs “non-cured”)
  - components mixed up with constant weights

So this is like mixture cure model?...

Actually, no...

- Mixture Cure Model
  - considers two components (“cured” vs “non-cured”)
  - components mixed up with constant weights
- Poly-hazard
  - Assumes that there are “competing risks” for the event
  - Overall hazard $=$ sum of competing/contributing hazards

So this is like mixture cure model?...

Actually, no...

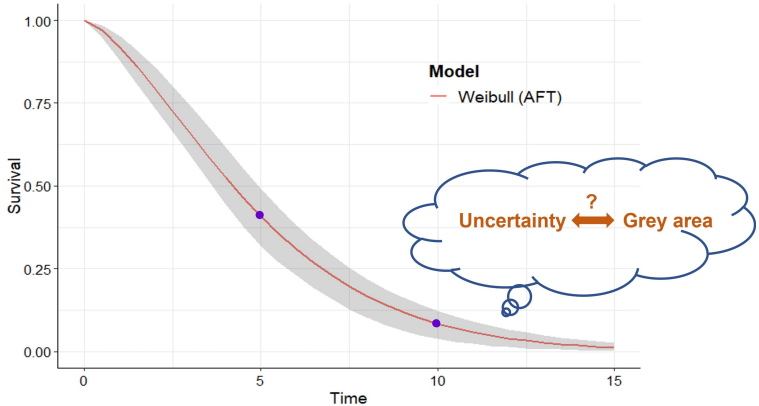
- Mixture Cure Model
  – considers two components (“cured” vs “non-cured”)
  – components mixed up with constant weights

- Poly-hazard
  – Assumes that there are “competing risks” for the event
  – Overall hazard $=$ sum of competing/contributing hazards

- Blended model
  – Similar to MCM BUT: weights change over time
  – Similar to poly-hazard: component-wise hazards sumed (using weighted average, determined by time-specific weights)

Uncertainty: external information

- Constraints to survival curve extrapolation
  1. $S(10|\theta) \approx 0.1$
  2. $S(5|\theta) \approx 0.4$, $S(10|\theta) \approx 0.1$



Shiny app

Modelling Assumptions

Mixting area [a, b]: Blended survival starts from observed data fitting (green), approaches to External info (blue) from timepoint a, and finally it is identical to the External info (blue) beyond timepoint b.

mix area: a

0 1 15

0 2 4 6 8 10 12 14 15

mix area: b

0 15

0 5 6 7 8 9 10 11 12 13 14 15

Mixing trend (beta function): two parameters control the way two distributions influence the blended curve. e.g. shape>scale means slow mixing speed, relatively shape<scale means fast choice.

Beta: shape

0.5 10

0.1 1.1 2.1 3.1 4.1 5.1 6.1 7.1 8.1 9.1 10

Beta: scale

0.5 10

0.1 1.1 2.1 3.1 4.1 5.1 6.1 7.1 8.1 9.1 10

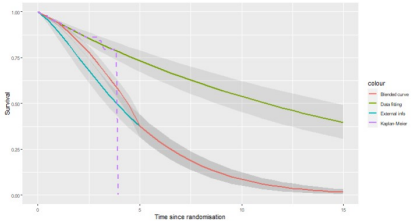
Uncertainty about your external assumptions determines the 95% interval of the survival estimates based on elicited beliefs (grey area around the blue curve). e.g. high level gives wide range

Uncertainty level of external info

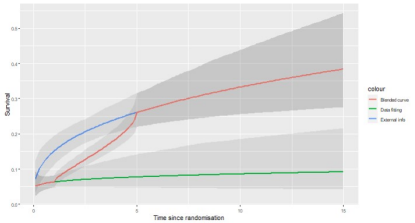
0 0.1 1

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Survival plot



Hazard plot



Summary

Advantages

- Overcomes the overly-optimistic constant treatment effect
- Sufficient flexibility with various plausible scenarios
- Less concerned about model selection

Limitations

- Elicited belief: probably a weak form of evidence, need long-term data
- Does not (yet) account for other kind of external knowledge...

Conclusion

- Less mature data create a big challenge for survival extrapolation
  - though many good techniques can characterise realistic hazard functions

Conclusion

- Less mature data create a big challenge for survival extrapolation
  - though many good techniques can characterise realistic hazard functions
- Possible solution – Bayesian framework for eliciting beliefs

Conclusion

- Less mature data create a big challenge for survival extrapolation
  – though many good techniques can characterise realistic hazard functions
- Possible solution – Bayesian framework for eliciting beliefs
- Blended curve is a simple and not computationally intensive method
  – to incorporate clinical opinion for long-term survival
- The method considers a wide range of plausible scenarios
  – the lack of data causes the uncertainty

Acknowledgements

- Gianluca Baio, PhD, University College London
- Nathan Green, PhD, University College London
- Victoria Paly, MHS, ICON plc
- Håvard Rue, PhD, King Abdullah University of Science and Technology

Email: zhaojing.che.19@ucl.ac.uk

Q & A