Survival analysis in decision modeling

The DARTH Workgroup

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Overview

- Motivation and introduction in Survival analysis
- Survival modeling
- Partitioned survival modeling
- Multistate models
- Advanced topiics
  - Mixture cure models
  - External evidence in survival models

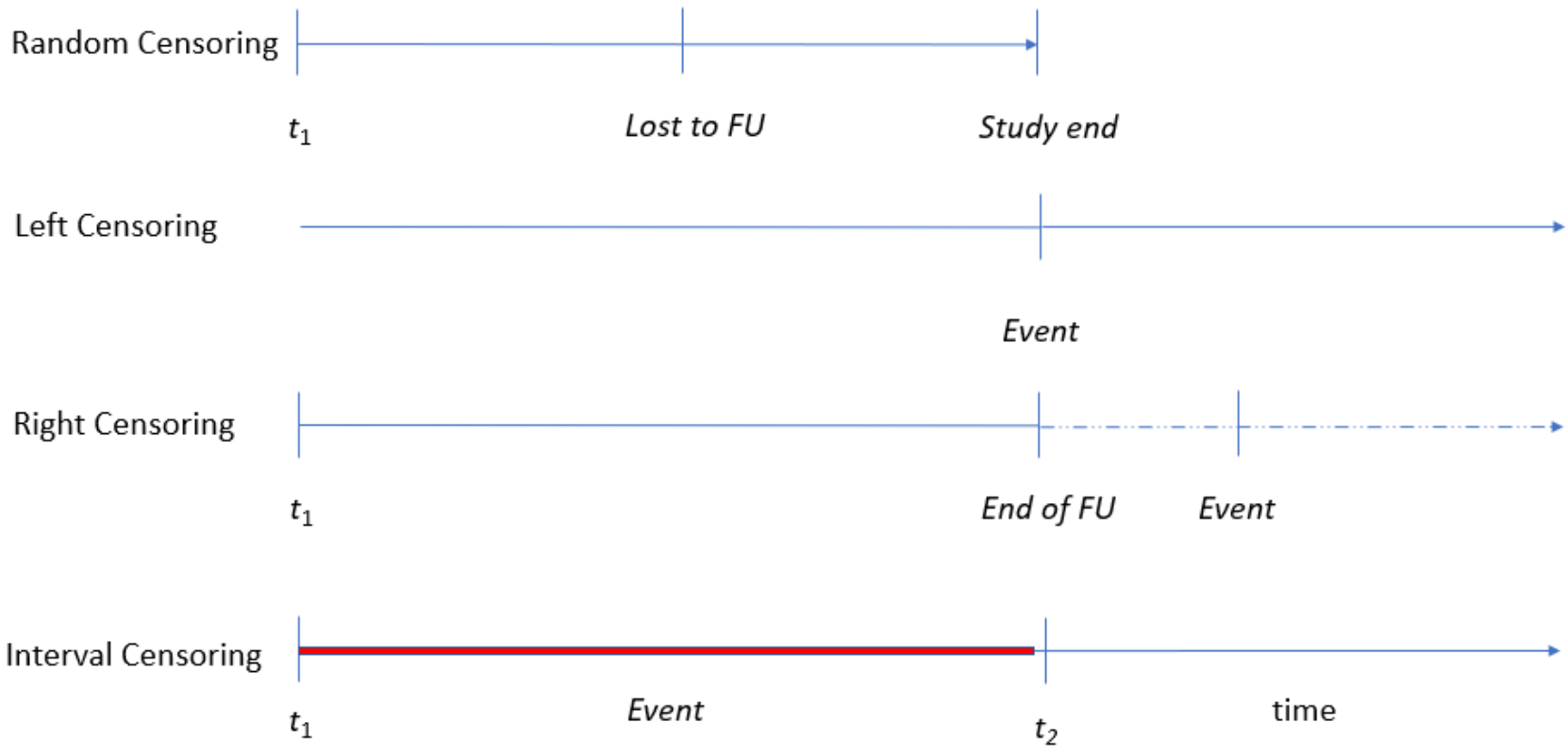
It's all about the data!

- RCT evidence often not sufficient for Health Technology Assesment (HTA)
  - Short follow up
  - Patients lost during follow up
  - Often not reflective of real world
  - Right skewed
  - Information "flowing" over intervals
  - Extrapolation often necessary

Bonus challenges in Oncology RCTs

- Overall Survival (OS), Progression-Free Survival (PFS)
- Trials powered to show differences on PFS and not OS
- Cross-over
- PFS and OS data are correlated
- Access to patient level OS data not always the case

Censoring


Random Censoring
t_1
Lost to FU
Study end
Left Censoring
Event
Right Censoring
t_1
End of FU
Event
Interval Censoring
t_1
Event
t_2
time

What is survival analysis

- Set of statistical methods that can handle:
  - Data skewness
  - Censoring
  - (Time-dependent) Covariates
  - State transition processes
  - Recurrent events
  - The expectation of cure
- Used for both inference and extrapolation
- Survival: the probability of not experiencing an event unit some time t

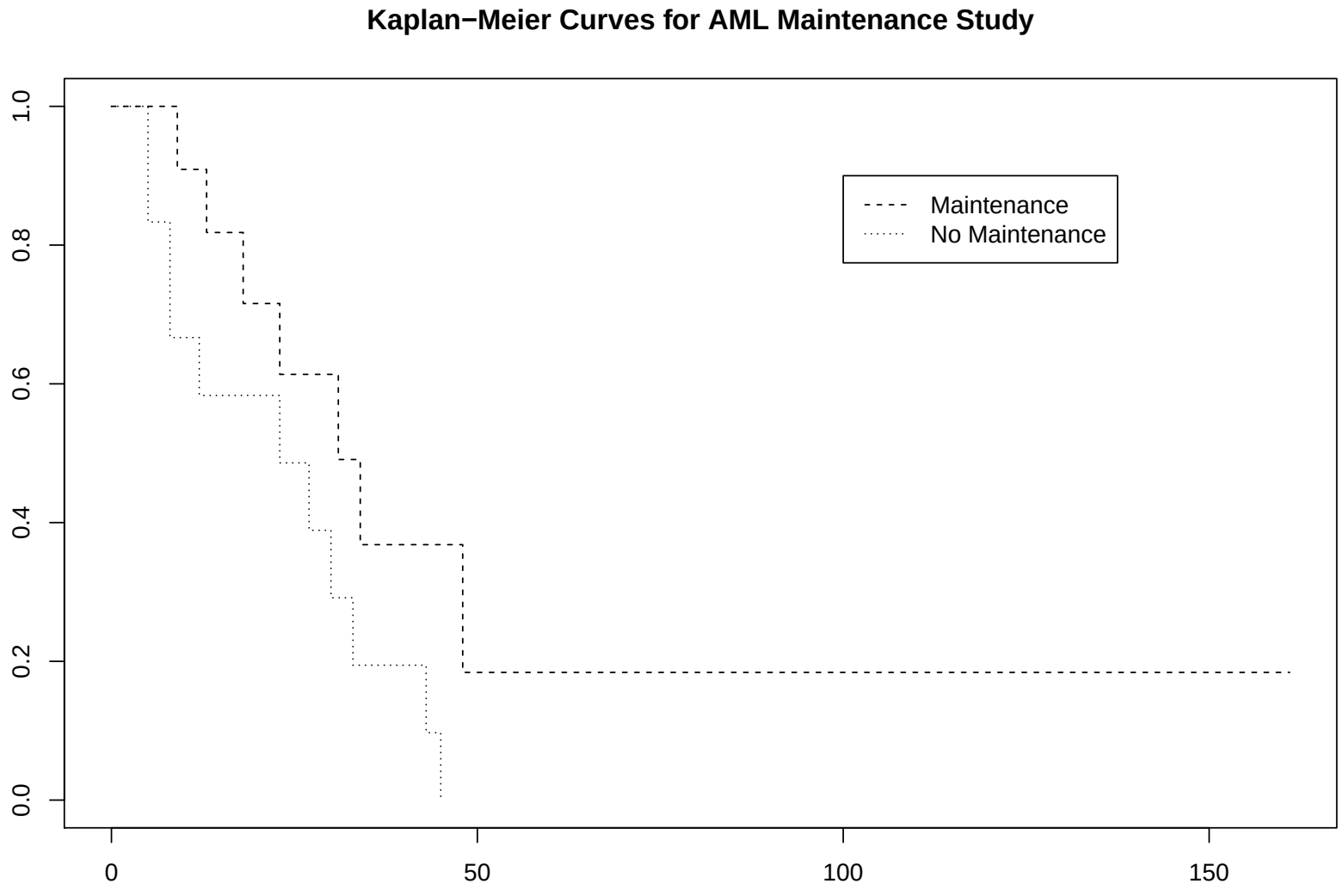
$$S(t) = Pr(T > t) = 1 - Pr(T \leq t)$$

Types of survival analysis models

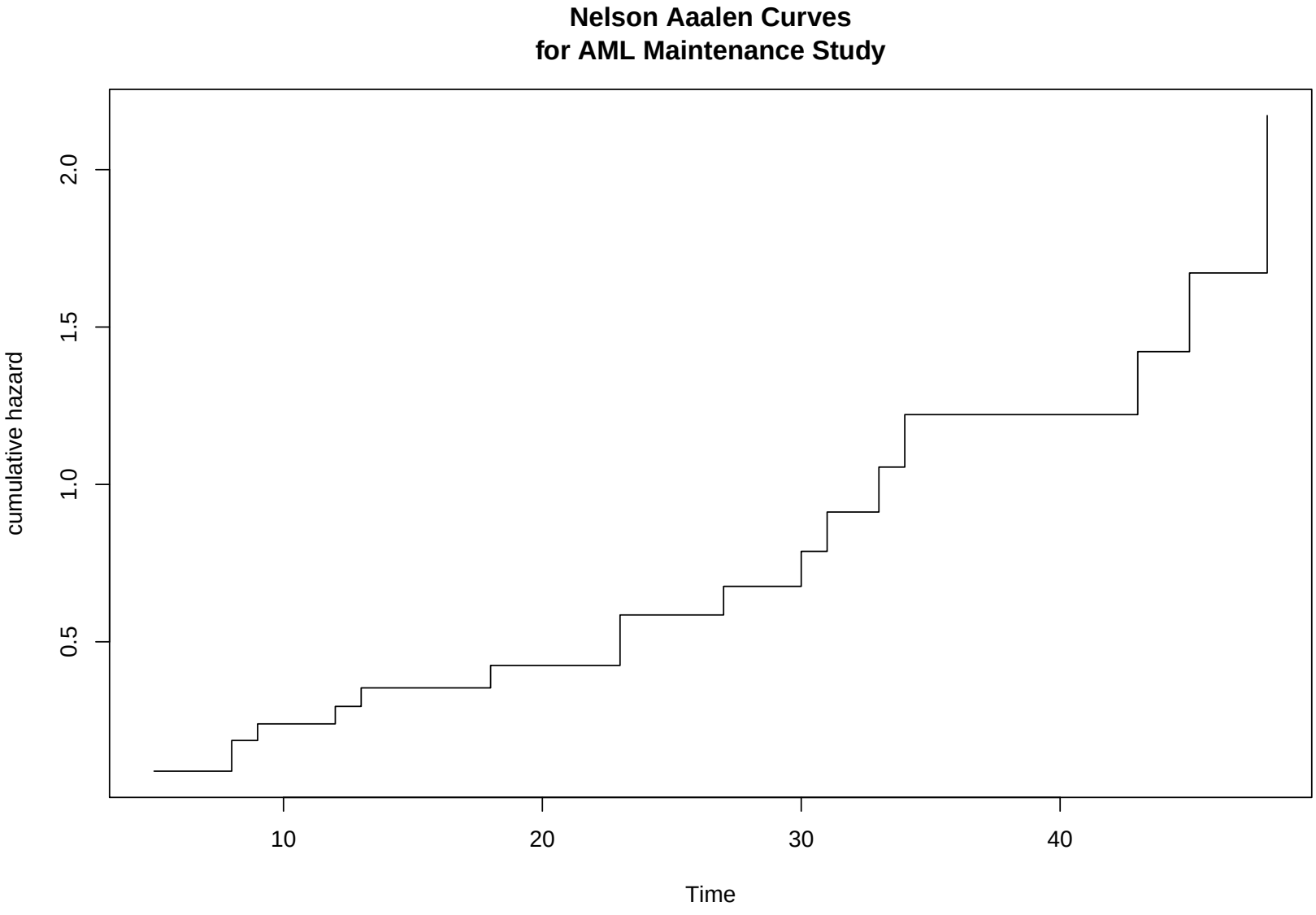
- Non-parametric models (e.g. Kaplan Meier)
- Semi-Parametric models (e.g. Cox Proportional Hazard)
- Parametric models (e.g. Accelerated Failure Time)

Non-Parametric models

- Kaplan Meier curves



- Nelson Aalen cumulative hazard



Semi- Parametric models

- Cox proportional hazard model
  - Hazard: the instantaneous risk of an event at time t, conditional on survival to that time.
- Semi:
  - Baseline hazard modelled non parametrically (i.e effect of time)
  - Covariate effects (β 's) modelled parametrically (like in a regression model)

Fully Parametric models

- Usually model time-to-event directly rather than hazard
- Resemble a regression model but can capture censoring
- Fit a distribution to the (observed) time-to-event data
  - 1 parameter : exponential
  - 2 parameter : Weibull, lognormal, gamma etc
  - 3, 4 parameter: Gen. gamma , Gen F etc
- Assumption that censored patients will follow similar patterns to the observed.
- Temporal extrapolation possible !

Choosing the "right" distribution

- Statistical considerations of goodness-of-fit
- Clinical plausibility
  - in-sample
  - extrapolations
  - out-of-sample

Goodness of fit metrics

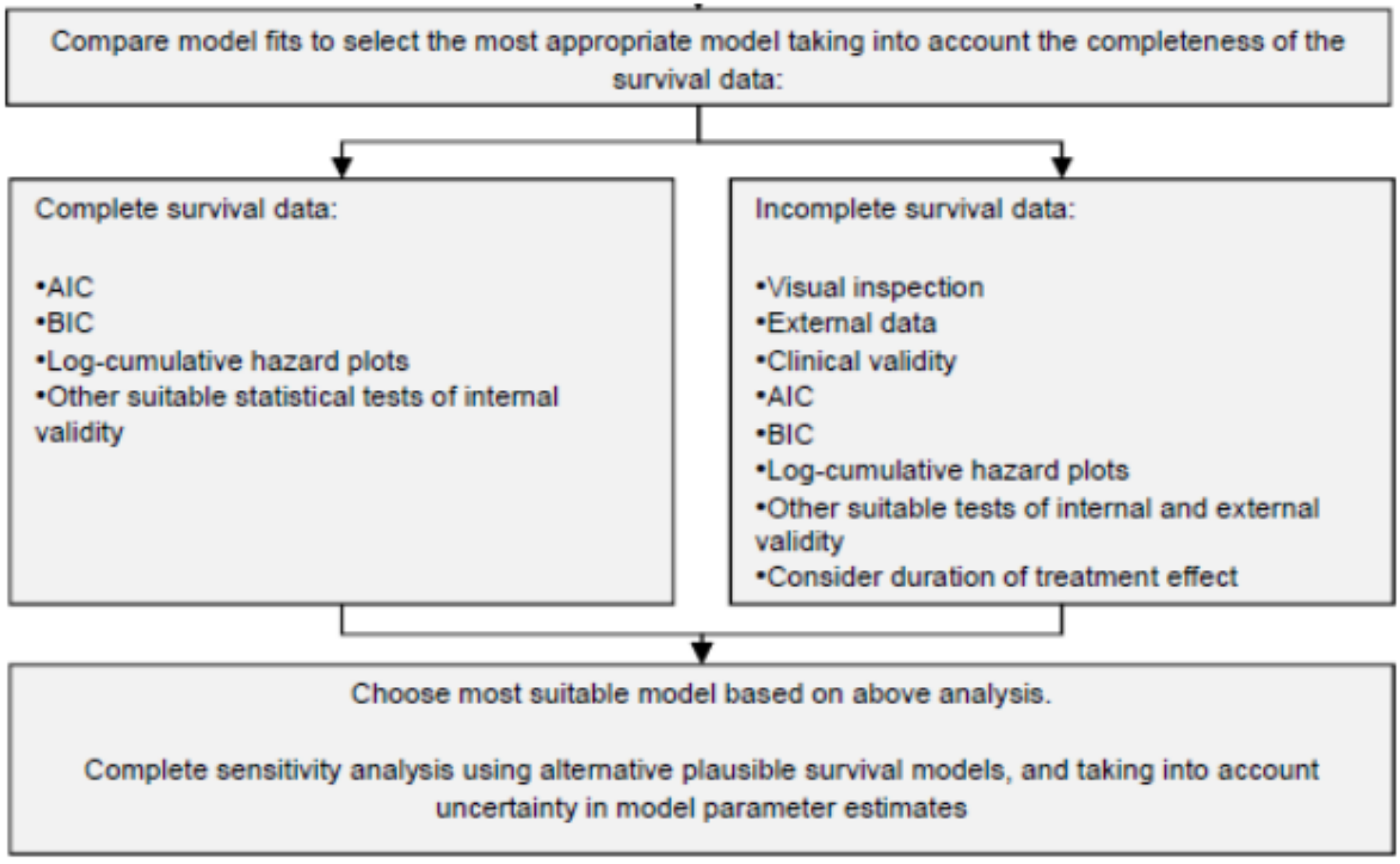
- Likelihood based metrics
- Akaike Information Criterion (AIC)
- Bayesian Information Criterion (BIC)
- Performance based metrics
- Sensitivity , Specificity
- (time dependent) Receiver Operating characteristic (ROC) curve
- Area Under the Curve (AUC)
- c- statistic

Choosing the "right" distribution

- NICE Decision Support Unit
- Latimer et al 2011 : Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data
  - **Survival Model Selection Process algorithm**:
    - *recommendations for how survival analysis can be undertaken more systematically. This involves fitting and testing a range of survival models and comparing these based upon internal validity (how well they fit to the observed trial data) and external validity (how plausible their extrapolated portions are)*

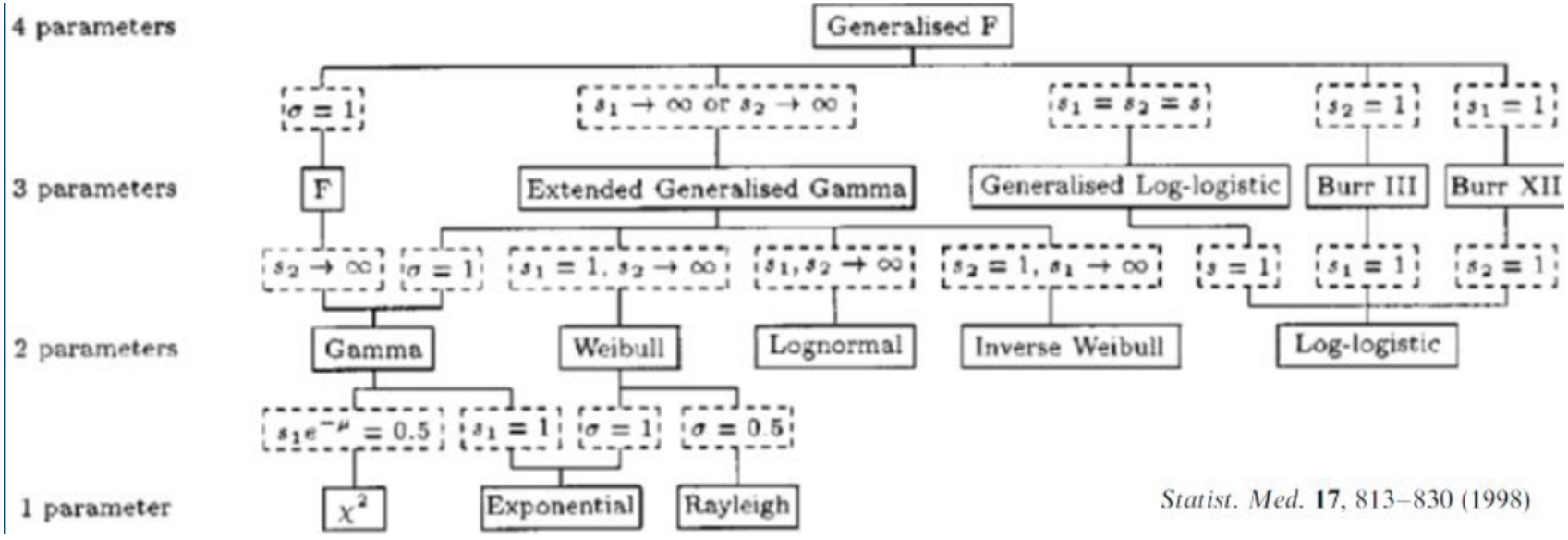
Choosing the "right" distribution

Latimer et al 2011 (DSU 14)



Flexible Survival models

- Multi - parameter distributions
  - Generalized Gamma
  - Generalized F
  - Data hungry - possibiliy of overfitting
  - Hypothesis testing possible



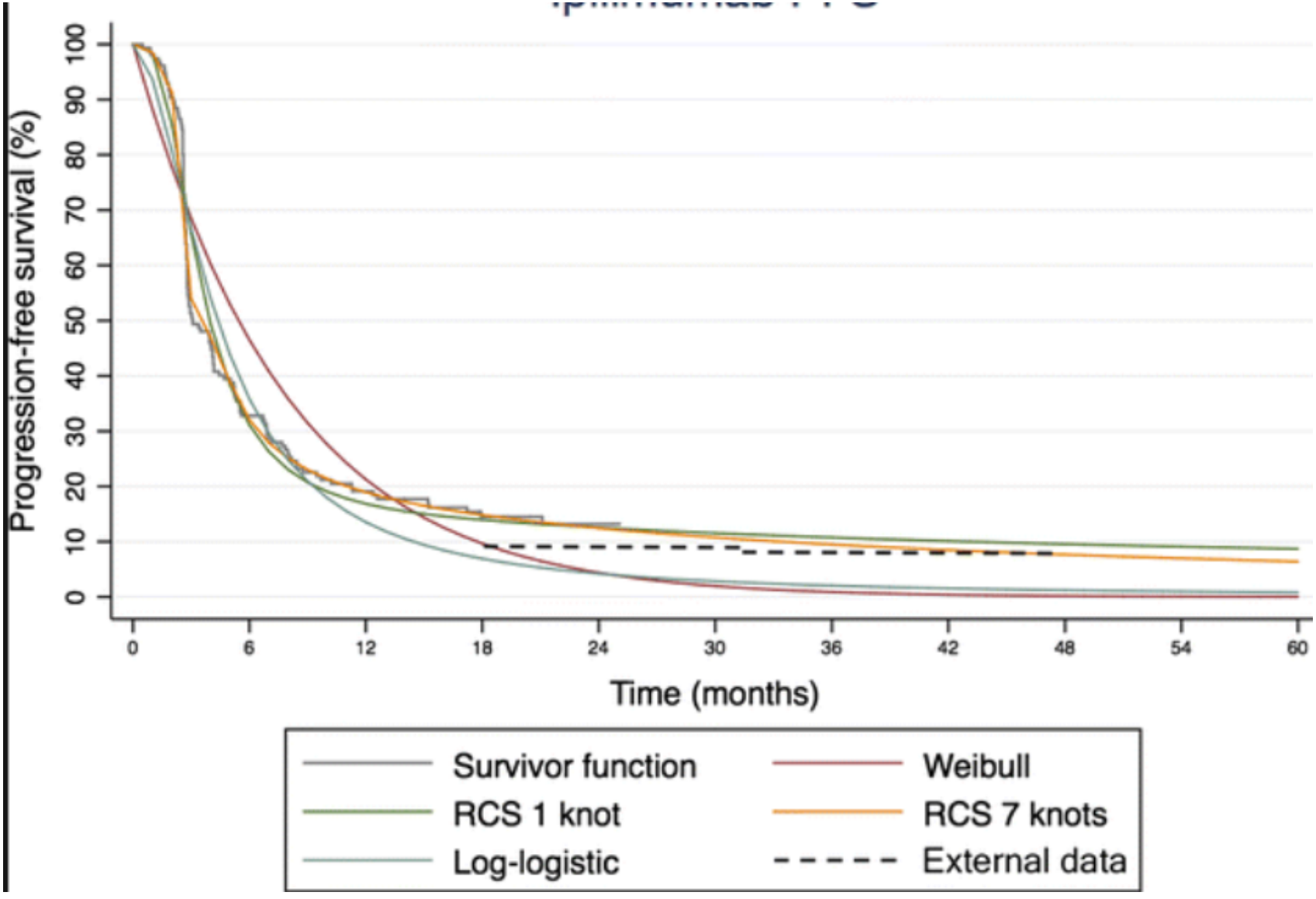
Statist. Med. **17**, 813–830 (1998)

Spline Survival models

- Survival models where the underlying hazard of an event is modelled as a smooth, piecewise polynomial function of time.
- Extrapolation of hazard possible
- Non-linear relation of time and hazard
- Conventionally *knots* are evenly spread on the (log)-time axis
- Overfitting with too many knots possible -sensitivity analysis
- AIC, BIC valid GoF tests

Spline Survival models

Gibson et al (Pharmacoeconomics, 2017)



Spline Survival models

From Gibson et al (Pharacoeconomcs, 2017)

Spline-based models using a limited number of knots can provide an acceptable fit to trial data and generate extrapolated estimates supported by longer term evidence, with results that are stable in response to changes in knot placement.

Approaches in extrapolation

Modeler faced with a more decisions: - Extrapolate using KM and "fitted" tails - Extrapolate using the fitted curve

- Fit seperate curves to the data
- Extrapolate treatment effect as relative
- What is the behaviour of the relative effect post trial?

Approaches in extrapolation

The Ends Justify the Mean: Outcome Measures for Estimating the Value of New Cancer Therapies

Andrew Davies, MSc[a], Andrew Briggs, DPhil[b], John Schneider, PhD[b], Adrian Levy, PhD[c], Omar Ebeid, MPH[b], Samuel Wagner, PhD[d], Srividya Kotapati, PharmD[d], Scott Ramsey, MD, PhD[e]

Approaches in extrapolation

- Extrapolate using KM and "fitted" tails

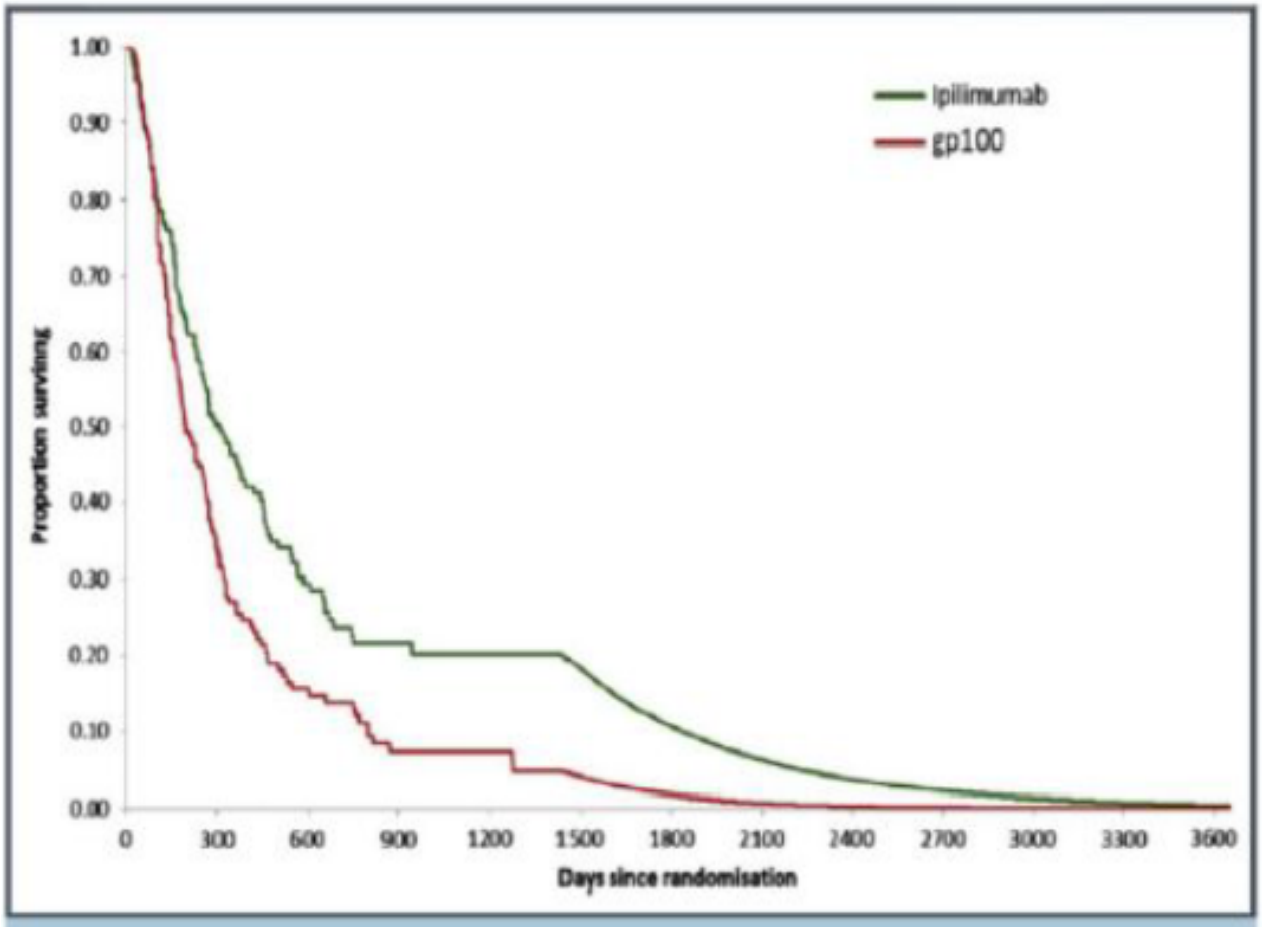


FIGURE 4: Case study showing empiric Kaplan-Meier curves and exponential extrapolation.

- Extrapolate using the fitted curve

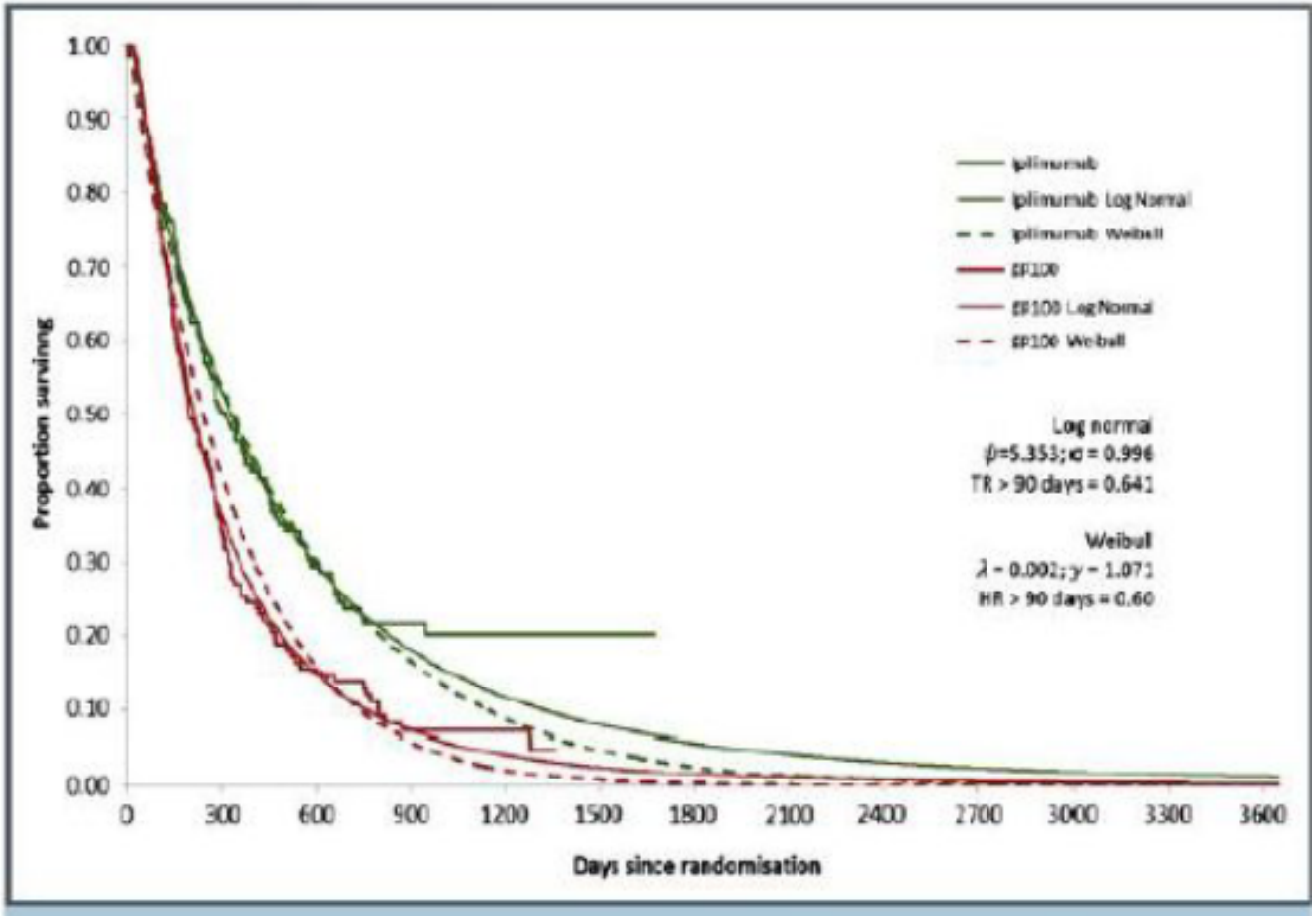
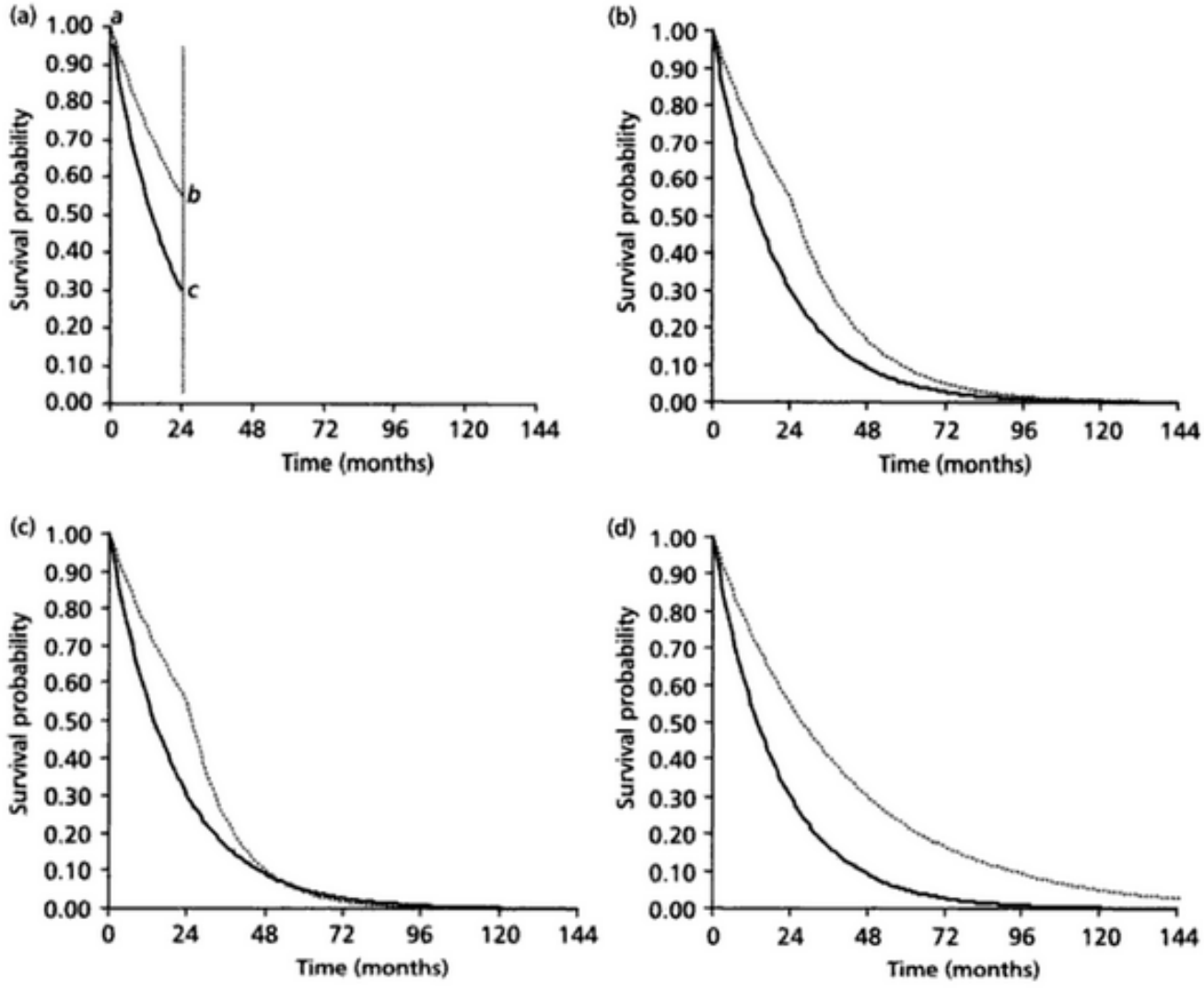


FIGURE 7: Case study showing empiric Kaplan-Meier curves and log-normal survivor functions.

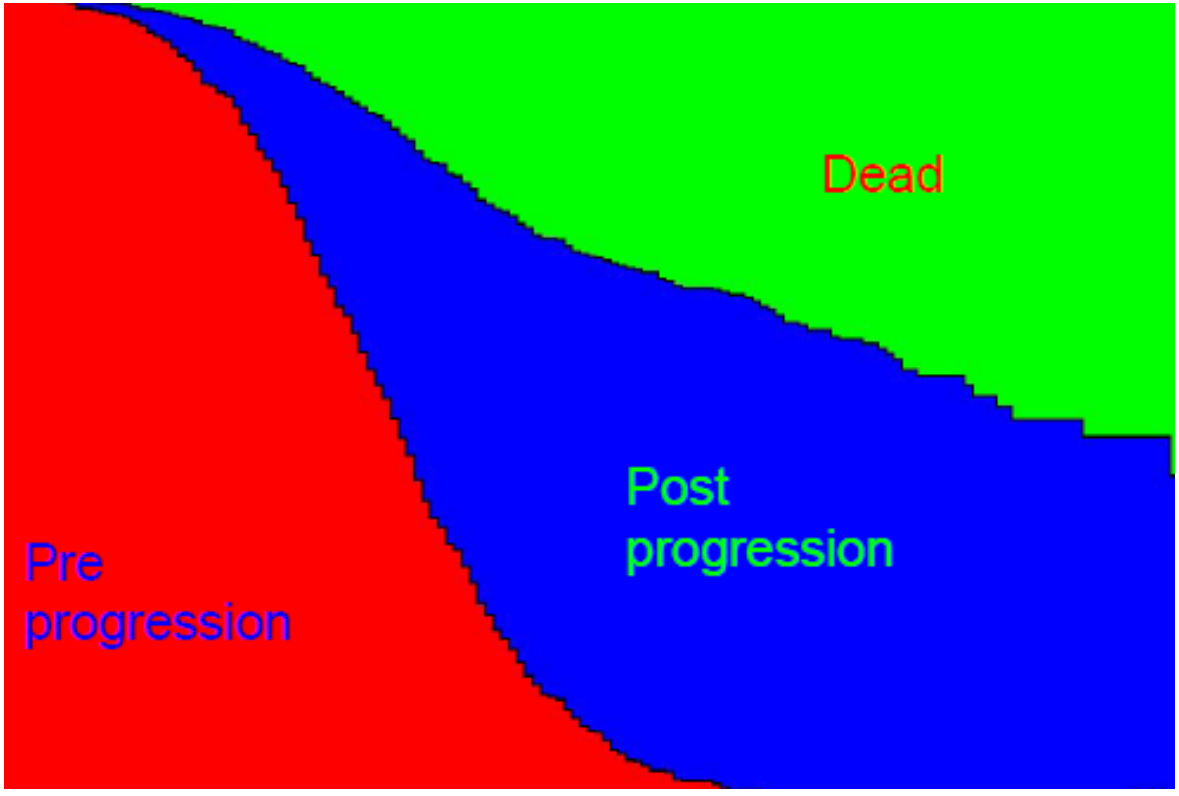
Extrapolating a relative treatment effect

Drummond, et al (2015). Methods for the economic evaluation of health care programmes. Oxford university press.



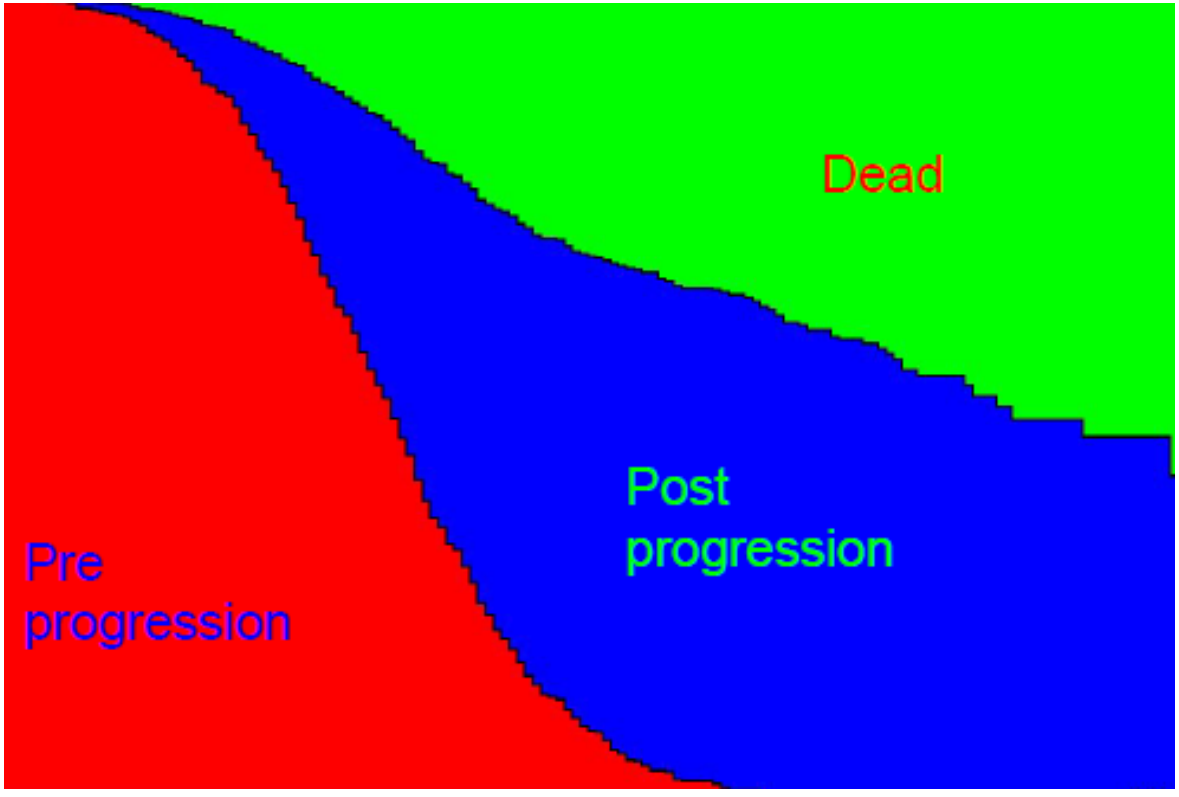
Partitioned survival models

- Form of a decision model that:
  - Considers evidence of (usually) OS and PFS
  - allocates the cohort across pre-progression, post-progression, death
- PFS and OS are modeled independently


Dead
Post
progression
Pre
progression

Partitioned survival models

- Mechanics:
  - Remain pre-progression: p(PFS)
  - Remain dead: 1 – p(OS)
  - Progressed: p(OS) - p(PFS)
- Implicit assumption: risk of dying is only a function of time



Less problematic with less censoring

Partitioned survival models - the updside

- Intuitively appealing
- Easy to communicate
- Easy to construct
- In-sync with what is commonly reported in RCTs
- Can be constructed using aggregate / graphic based data
- In-sync with methods of cross-over
- PSMs work great for cases where the whole cohort is observed until event of interest (unlikely in the vast majority of the cases)

Partitioned survival models - the downside

- OS and PFS are falsely assumed independent
- Cohort cannot transition back to a healthier state.
- 3-state PSM cannot distinguish the origin of the cohort moving to the dead state (progresed -> death vs preprogession -> death)
- In the presence of censoring:
  - Projected trajectory of state occupancy after end of follow up only informed by the observed trajectory
  - Poor performance when trends in the within trial period may not continue in the extrapolation period

Partitioned survival models - the criticism

Woods et al 2017 (DSU 19)

NICE DSU TECHNICAL SUPPORT DOCUMENT 19:

PARTITIONED SURVIVAL ANALYSIS FOR DECISION MODELLING IN HEALTH CARE: A CRITICAL REVIEW

REPORT BY THE DECISION SUPPORT UNIT

2 June 2017

Beth Woods[1], Eleftherios Sideris[1], Stephen Palmer[1], Nick Latimer[2], Marta Soares[1]

[1]Centre for Health Economics, University of York, York, UK
[2] School of Health and Related Research, University of Sheffield, UK

Williams et al 2017 (MDM)

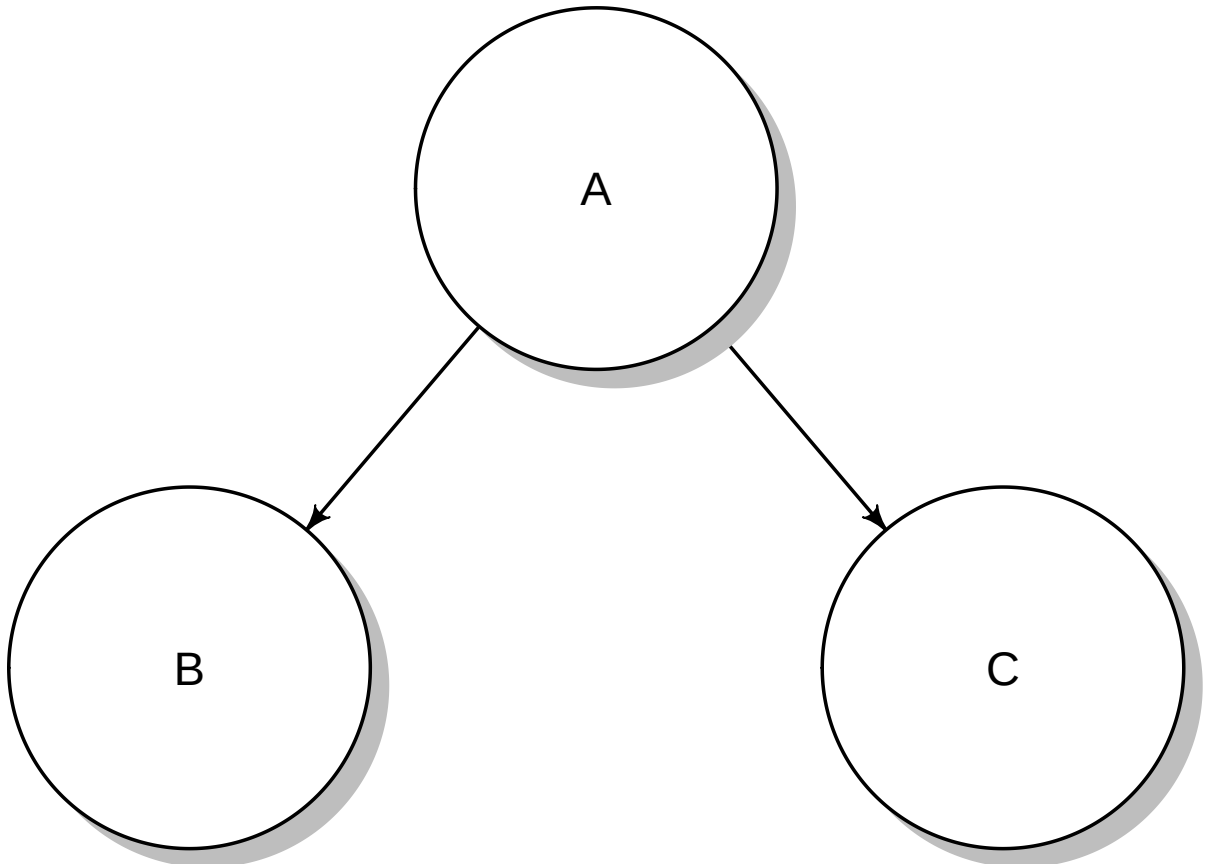
MEDICAL DECISION MAKING/MAY 2017 ORIGINAL ARTICLE

Estimation of Survival Probabilities for Use in Cost-effectiveness Analyses: A Comparison of a Multi-state Modeling Survival Analysis Approach with Partitioned Survival and Markov Decision-Analytic Modeling

Claire Williams, MSc, James D. Lewsey, PhD, Daniel F. Mackay, PhD, Andrew H. Briggs, DPhil

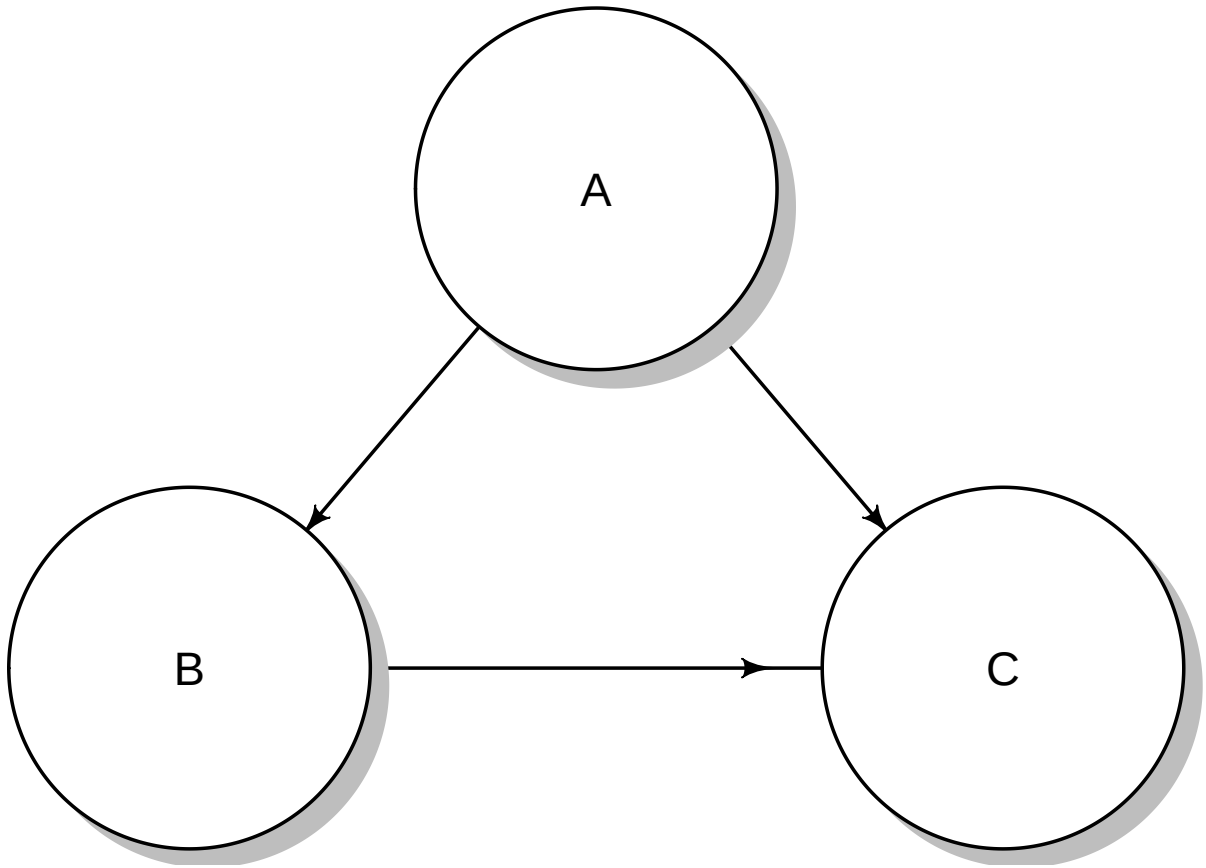
Competing Risks

- Underlying assumption in survival analysis:
  - If we could follow censored individuals long enough they would experience the event of interest.
- Event B (progression) affecs population size at risk for the competing event C


A
B
C

Multistate modeling

- Extended form of competing risks
- Multivariate survival analysis



Multistate modeling

- Extended form of competing risks
- Multivariate survival analysis
- Can incorporate:
  - Transition specific covariates
  - Recurrent events
- Can work with
  - Patient-level data (best)
  - Digitized / interval censored data (. . . not best)

Multistate modeling

Fitted in two ways:

1. separate models for each trasition

- recurrent events
- covariates
- seperate dataset for each (non-saturating) state
- "naive" assumption of censoring when competing event occurs
- easy to fit in R `flexsurv` and `mstate`

Multistate modeling

Fitted in two ways:

2. Joint multivariate model for all transitions - Powerfull!
   - Mislclassification errors
   - Latent states
   - Interval censoring
   - Continuous time

Drawbacks: - Difficult to converge - Limited options wrt assumed distributions (exponential)

Can be fitted through `msm` and `flexsurv`

Multistate modeling

Journal of Statistical Software

May 2016, Volume 70, Issue 8. *doi: 10.18637/jss.v070.i08*

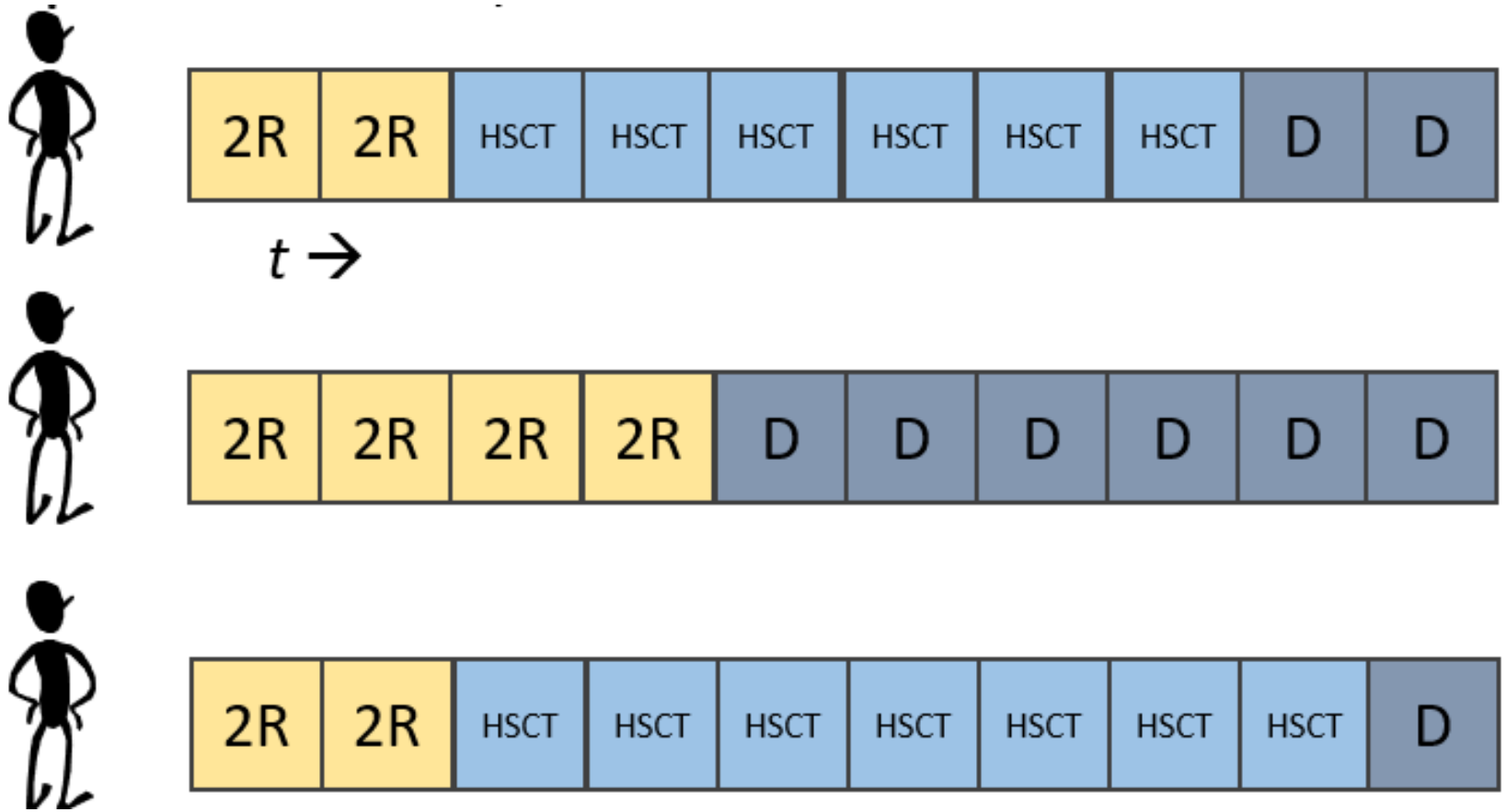
flexsurv: A Platform for Parametric Survival Modeling in R

Christopher H. Jackson
MRC Biostatistics Unit

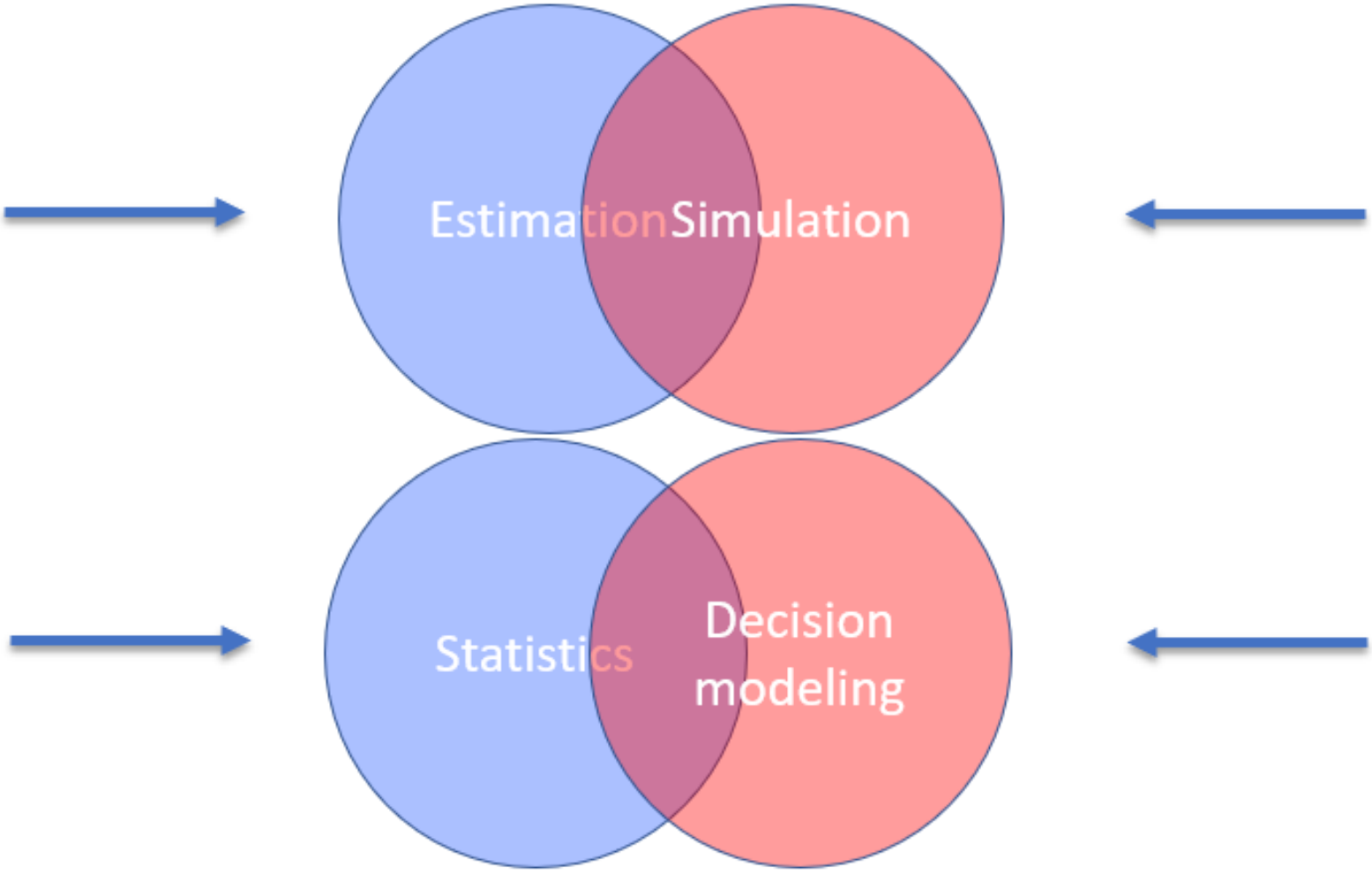
Great resource for both survival fitting and multistate models

Multistate & microsimulation

- Multistate models allow for time-dependent transition probabilities
- When dependence on time-in-state partioned survival / markov models are inadequate
- Necessary solution: Individual level simulation modeling



Multistate modeling



Multistate modeling

Natalizumab (Tysabri®) for the Treatment of Adults with Highly Active Relapsing Remitting Multiple Sclerosis

Biogen Idec Single Technology Appraisal (STA) Submission to The National Institute for Health and Clinical Excellence

Document name:	Natalizumab in HARRMS_FINAL.doc
Product:	Tysabri® (natalizumab)
Manufacturer:	Biogen Idec
Document written by:	Biogen Idec, Heron Evidence Development
Document customer:	The National Institute for Health and Clinical Excellence (NICE)
Document purpose:	To present the clinical and cost-effectiveness of natalizumab in highly active relapsing remitting multiple sclerosis to NICE
Confidential Information:	Note that all confidential information within the submission has been removed

External data and survival models

Given short term follow up in RCTs, survival extrapolations can be informed by external data

- Adjustment of all-cause mortality using life-tables
- Expert opinion on plausibility

Other sources of external data:

- longer follow-up on a different RCT
- disease registry
- administrative data

External data and survival models

Observational data

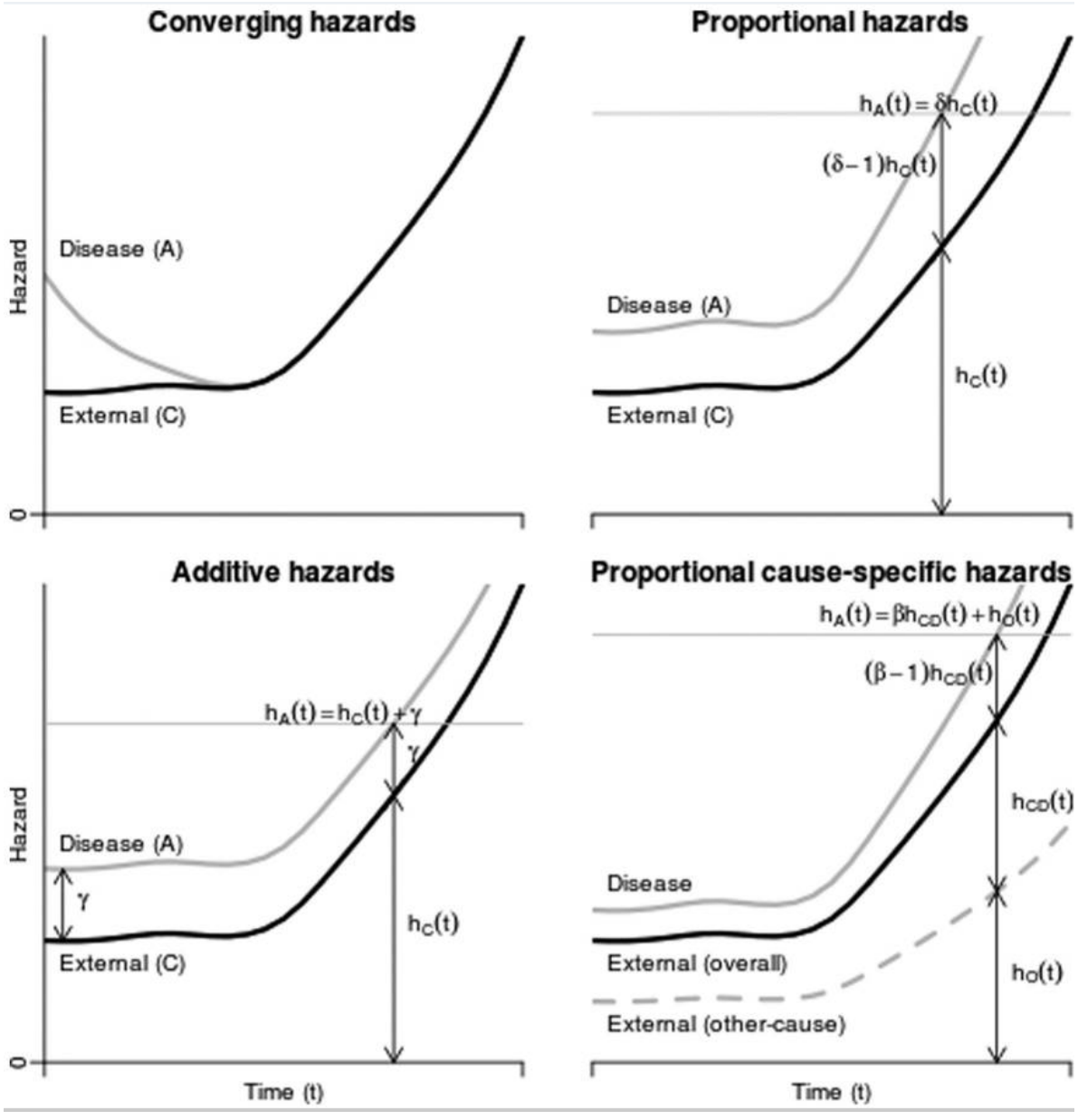
- possibly more representative of the real world
- at risk for (unmeasured) confounding

ORIGINAL ARTICLE

Extrapolating Survival from Randomized Trials Using External Data: A Review of Methods

Christopher Jackson, PhD, John Stevens, PhD, Shijie Ren, MPhil, PhD, Nick Latimer, PhD, MSc, Laura Bojke, PhD, MSc, Andrea Manca, PhD, MSc, Linda Sharples, PhD

External data and survival models

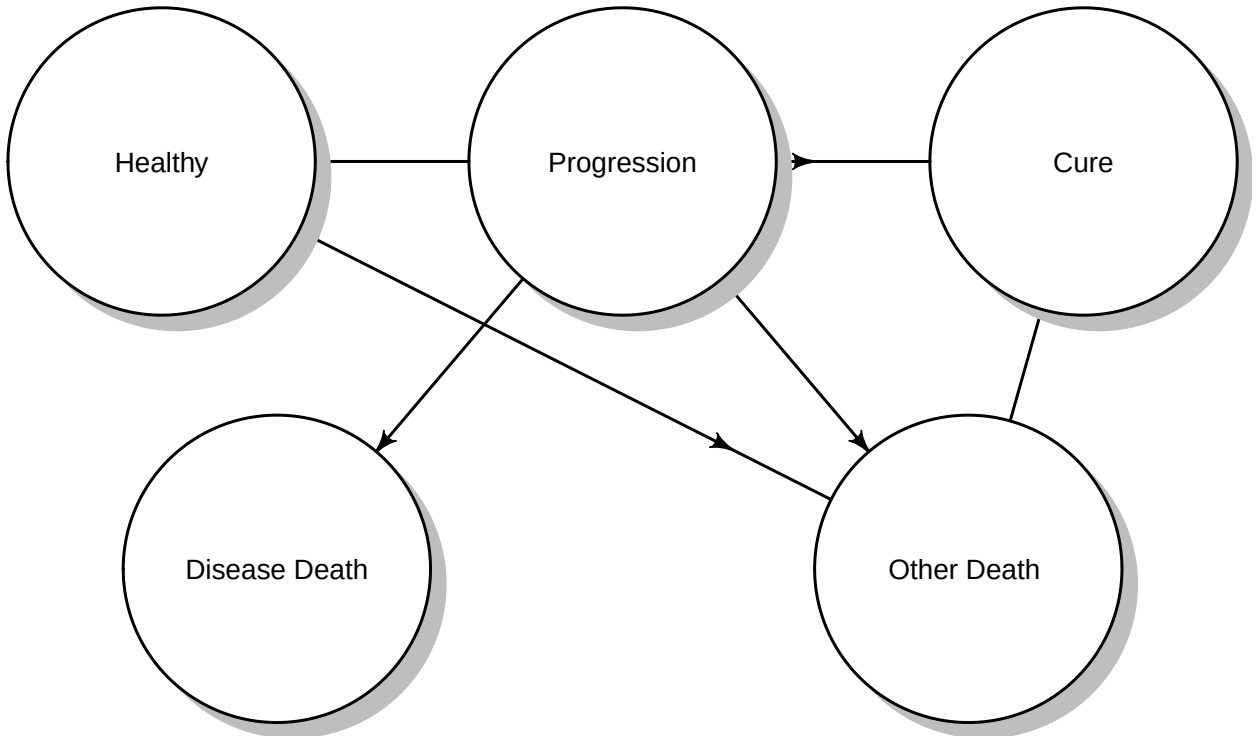


Mixture Cure Models - Main Points

- Therapies with the possibility of cure pose a modeling challenge
- e.g. plateau on immotherapy survival curves
- Extrapolation challenging without external information
- Traditional methods: Underestimation more likely than over estimation of the effect

Mixture Cure Models - Main Points

- extension of survival models where a proportion of the population is assumed to be "cured"
  - non-cured fraction at risk of progression and death informed by the trial
  - cured fraction at risk of death informed by external data.



Mixture Cure Models - Estimation

- Cure rate models a promising solution but the cure faction difficult to estimate
- Can be fitted in both R and SAS
- Guidance is lacking but given the popularity soon to come!

Mixture Cure Models - Validity

- Paucity of applications in HTA

Comparative-Effectiveness Research/HTA

Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study

Ash Bullement, MSc [1,2,], Nicholas R. Latimer, PhD [3], Helen Bell Gorrod, PhD [3]*

[1]BresMed Health Solutions, Sheffield, UK; [2]Delta Hat, Nottingham, UK; [3]School of Health and Related Research, University of Sheffield, Sheffield, UK

- Recently shown to be more appropriate than conventional modeling (n of 1)

Thank you!