Survival Analysis in Economic Evaluation

The DARTH Workgroup

Overview

- Motivation and introduction in Survival Analysis
- Survival modeling
- Non-Parametric modeling
- Semi-Parametric modeling
- Fully Parametric modeling
- Multistate models

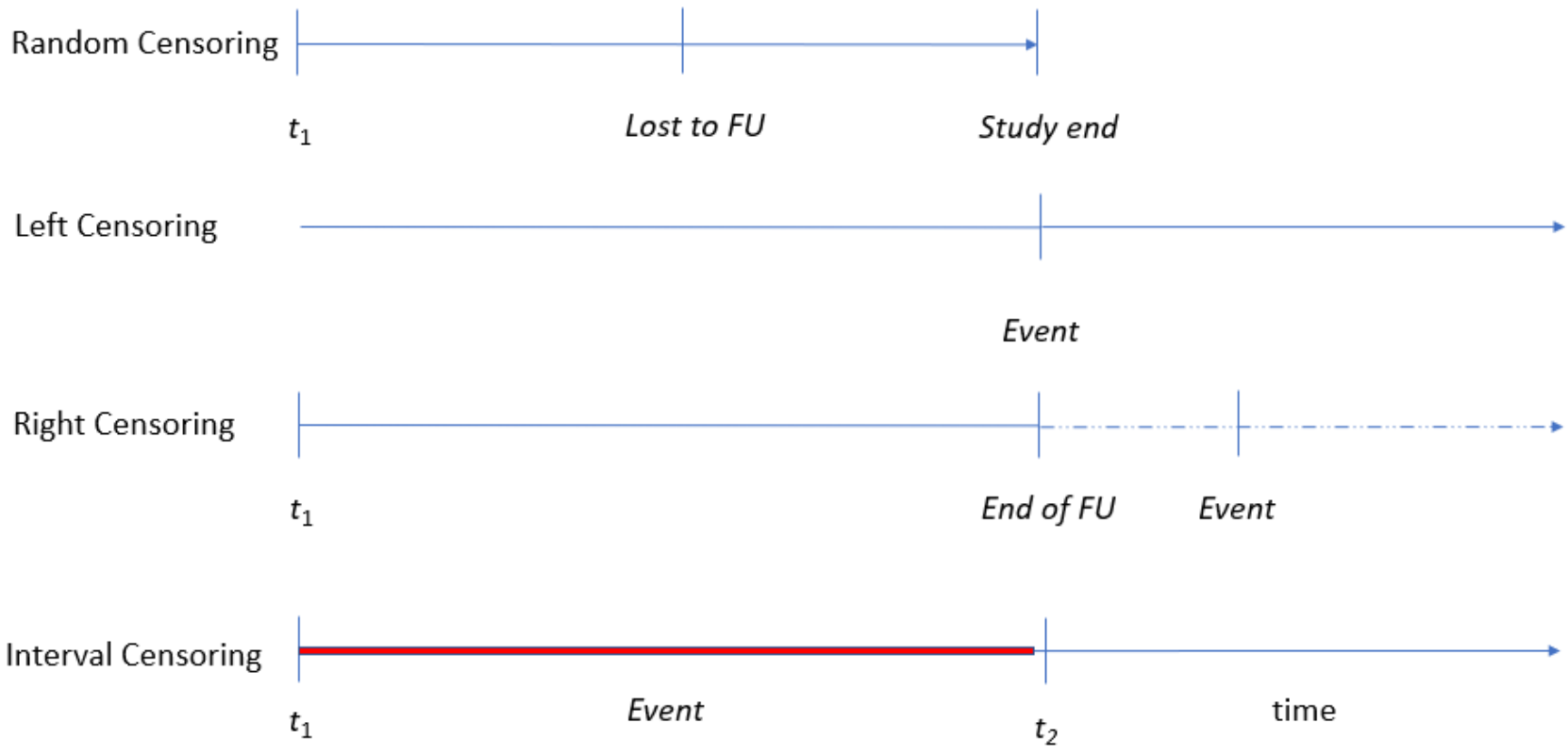
It's all about the data!

- 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

Infromative Censoring

The case where survival time is dependent with whatever causes the censoring. Example: A patient in a community study is censored because they are hospitalized (hospitalization indicates severity)

In most of the examples throughout we will make the assumption of non-informative censoring

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

Key Concepts in survival analysis

- survival to time T: the random variable capturing time since the beginning of the event.
- Survival: the probability of not experiencing an event unit some time t $S(t) = Pr(T > t) = 1 - Pr(T \leq t)$
- Cumulative density function:

$$F(t) = Pr(T \leq t)$$

$$F(t) = 1 - S(t)$$

- Hazard function (the instantaneous rate of the event): $h(t) = \lim_{\delta t \to 0} \frac{1}{\delta t} \frac{F(t+\delta t) - F(t)}{S(t)}$

turns out $h(t) = \frac{f(t)}{S(t)}$

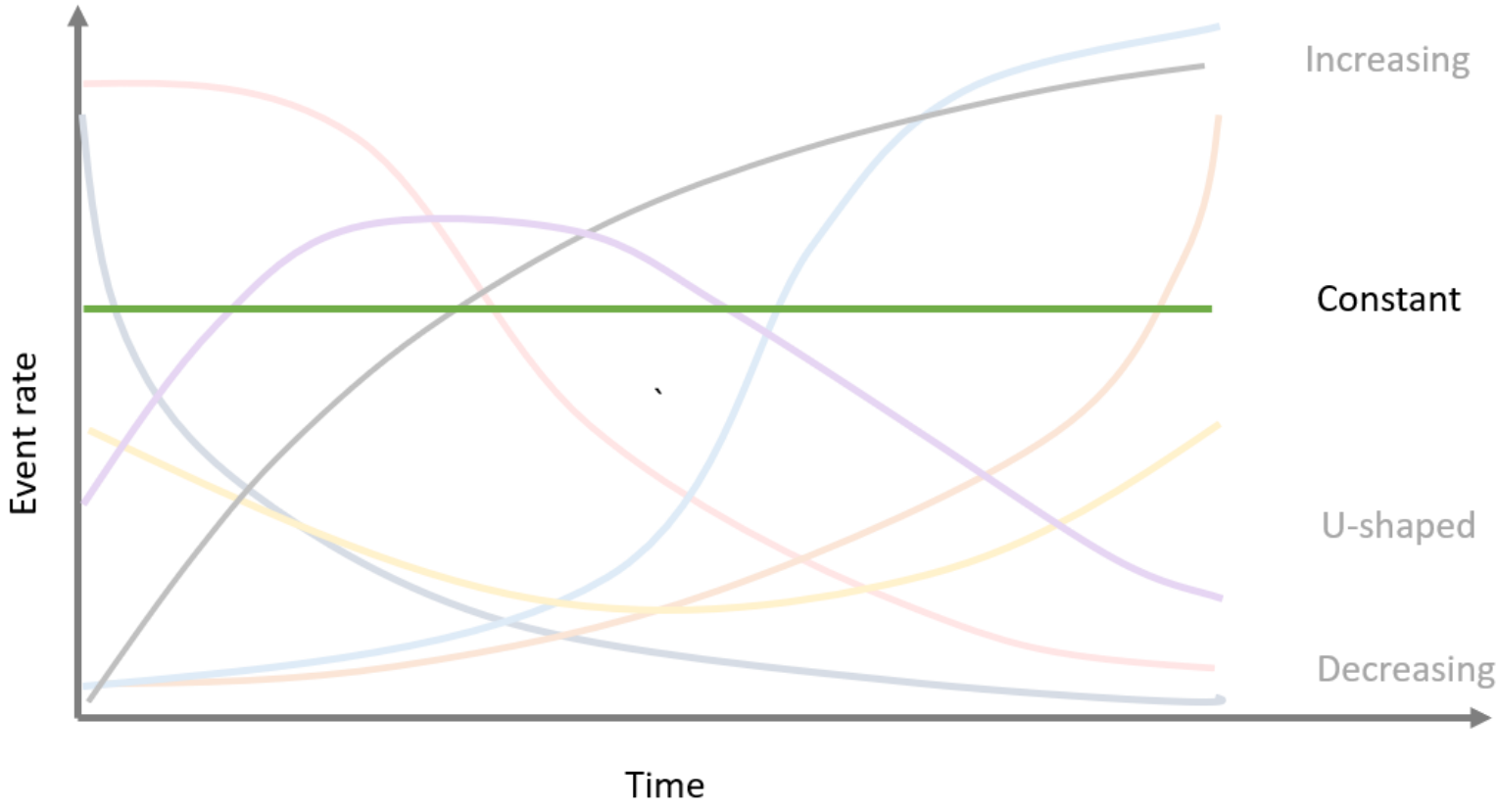
- Cumulative hazard $H(t) \int_0^t h(x)dx$

as well as $S(t) = e^{-H(t)}$

Example: the exponential distribution

- $H(t) = \lambda t$
- $S(t) = exp(-\lambda t)$
- $f(t) = \lambda exp(-\lambda t)$
- Weibull , gamma, lognormal etc. . .

Some shapes of hazards



common distributions and hazard shapes

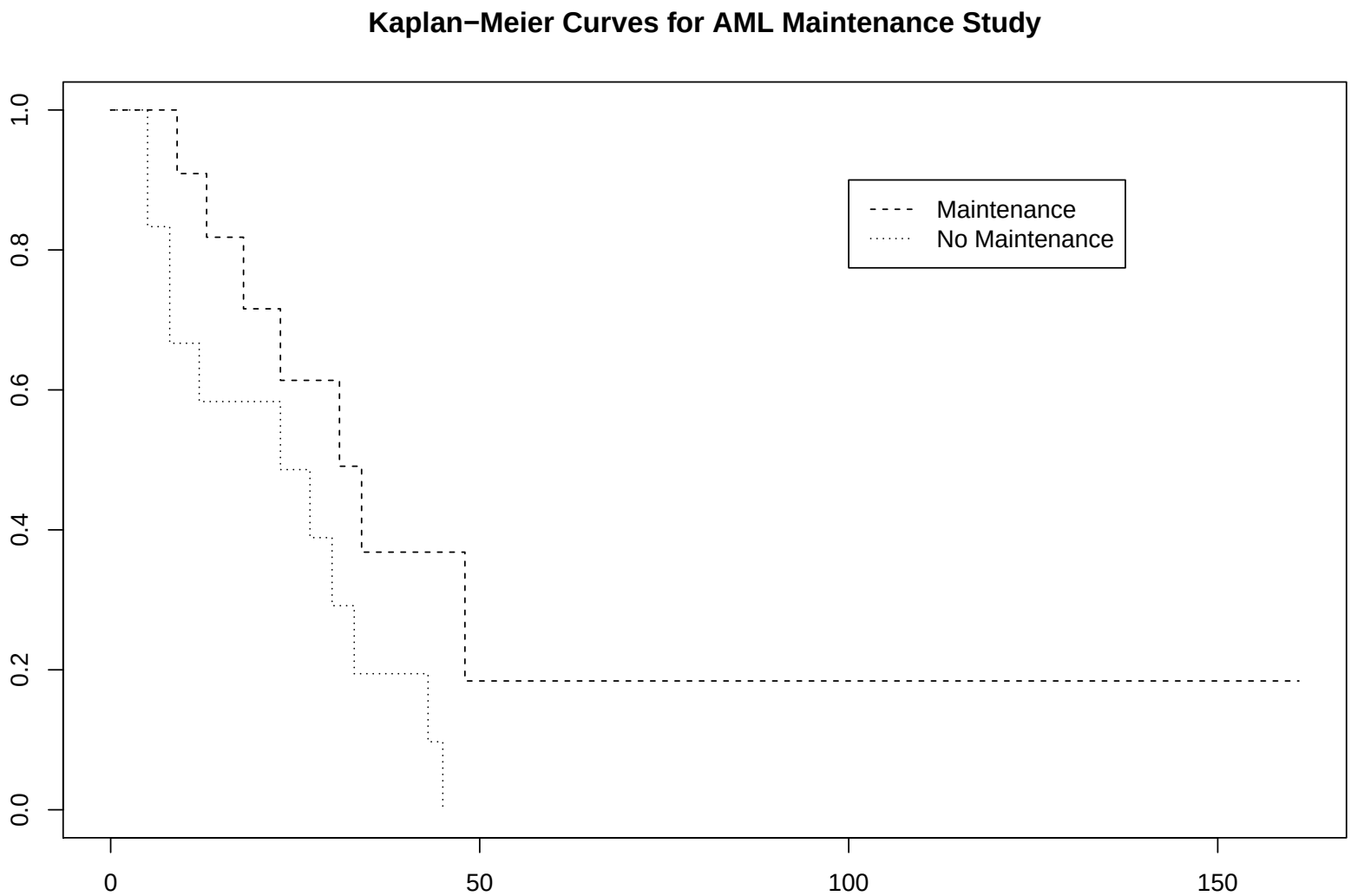
- Exponential:constant hazard
- Weibull: hazard monotonically increases/decreases
- Gompertz: hazard monotonically increases/decreases, but the rate of change is exponential
- Log-logistic, log normal: hazard monotonically increases, and can then decrease

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

- known as the "product-limit" estimator. The most used survival analysis method
- makes no parametric assumption on the data



Non-Parametric models

```
Call: survfit(formula = Surv(time, status) ~ x, data = aml)

                x=Maintained
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    9     11       1    0.909  0.0867        0.7541        1.000
   13     10       1    0.818  0.1163        0.6192        1.000
   18      8       1    0.716  0.1397        0.4884        1.000
   23      7       1    0.614  0.1526        0.3769        0.999
   31      5       1    0.491  0.1642        0.2549        0.946
   34      4       1    0.368  0.1627        0.1549        0.875
   48      2       1    0.184  0.1535        0.0359        0.944

             x=Nonmaintained
 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    5     12       2   0.8333  0.1076        0.6470        1.000
    8     10       2   0.6667  0.1361        0.4468        0.995
   12      8       1   0.5833  0.1423        0.3616        0.941
   23      6       1   0.4861  0.1481        0.2675        0.883
   27      5       1   0.3889  0.1470        0.1854        0.816
   30      4       1   0.2917  0.1387        0.1148        0.741
   33      3       1   0.1944  0.1219        0.0569        0.664
   43      2       1   0.0972  0.0919        0.0153        0.620
   45      1       1   0.0000     NaN           NA           NA
```

Non-Parametric models - testing

- We can use a non parametric test to understand if group A lives longer than group B
- long-rank test: is the difference in survival times statistically different?
- relying on a χ^2 distribution

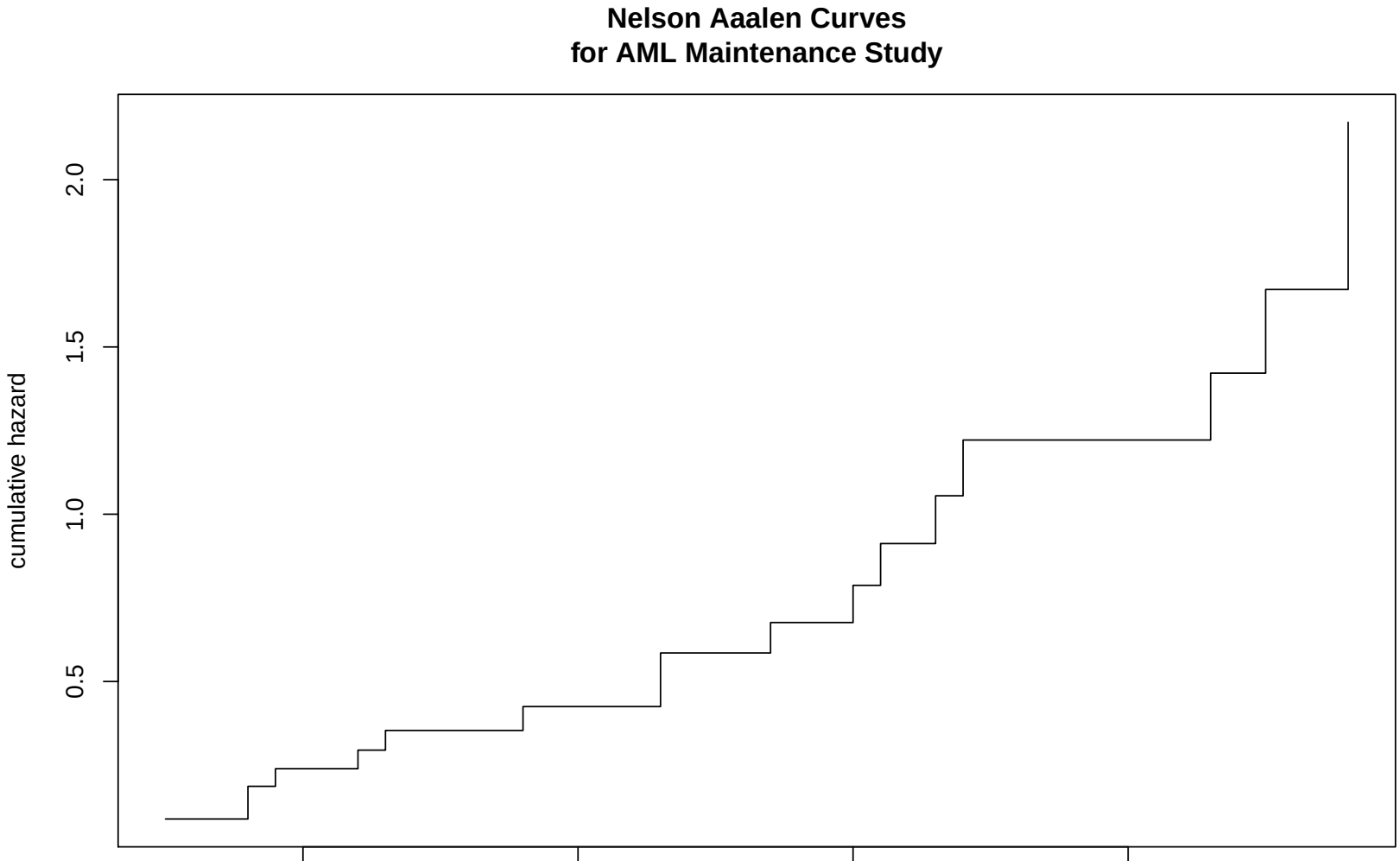
```
Call:
survdiff(formula = Surv(time, status) ~ x, data = aml)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
x=Maintained    11        7    10.69      1.27       3.4
x=Nonmaintained 12       11     7.31      1.86       3.4

 Chisq= 3.4  on 1 degrees of freedom, p= 0.07
```

Non-Parametric models

- Often, more intuitive to look at the results on the cumulative hazard rate
- Nelson Aalen cumulative hazard is the most common non parametric estimator



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)

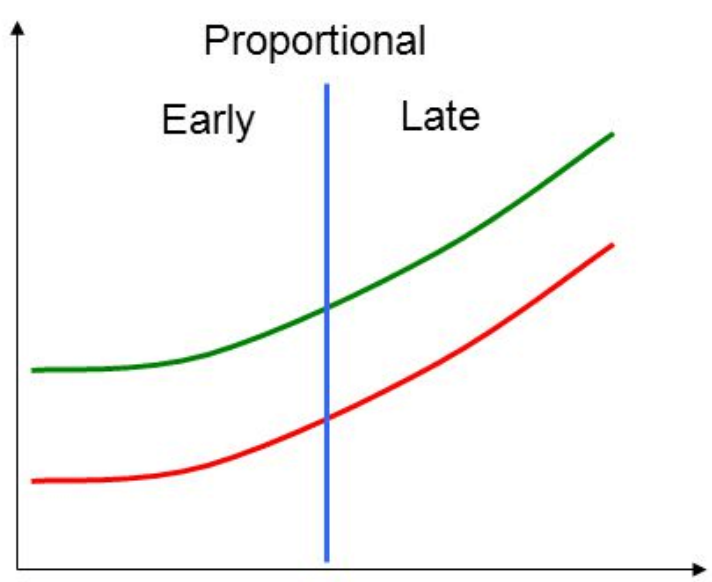
$h(t) = h_0(t)exp(X\beta)$ where $h_0(t)$ is estimated non-parametrically

Notice that the effect of the covariates is proportional on the baseline hazard..(that's why "proportional hazard" model)

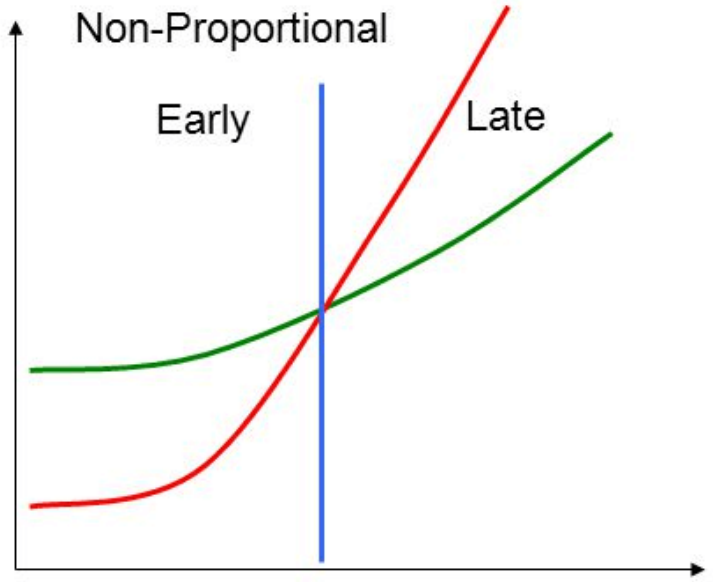
The assumption of proportional hazards

Proportional Hazard Assumption

- In a piecewise model, coefficients would differ in non-proportional models



Here, the effect is the same in both time periods

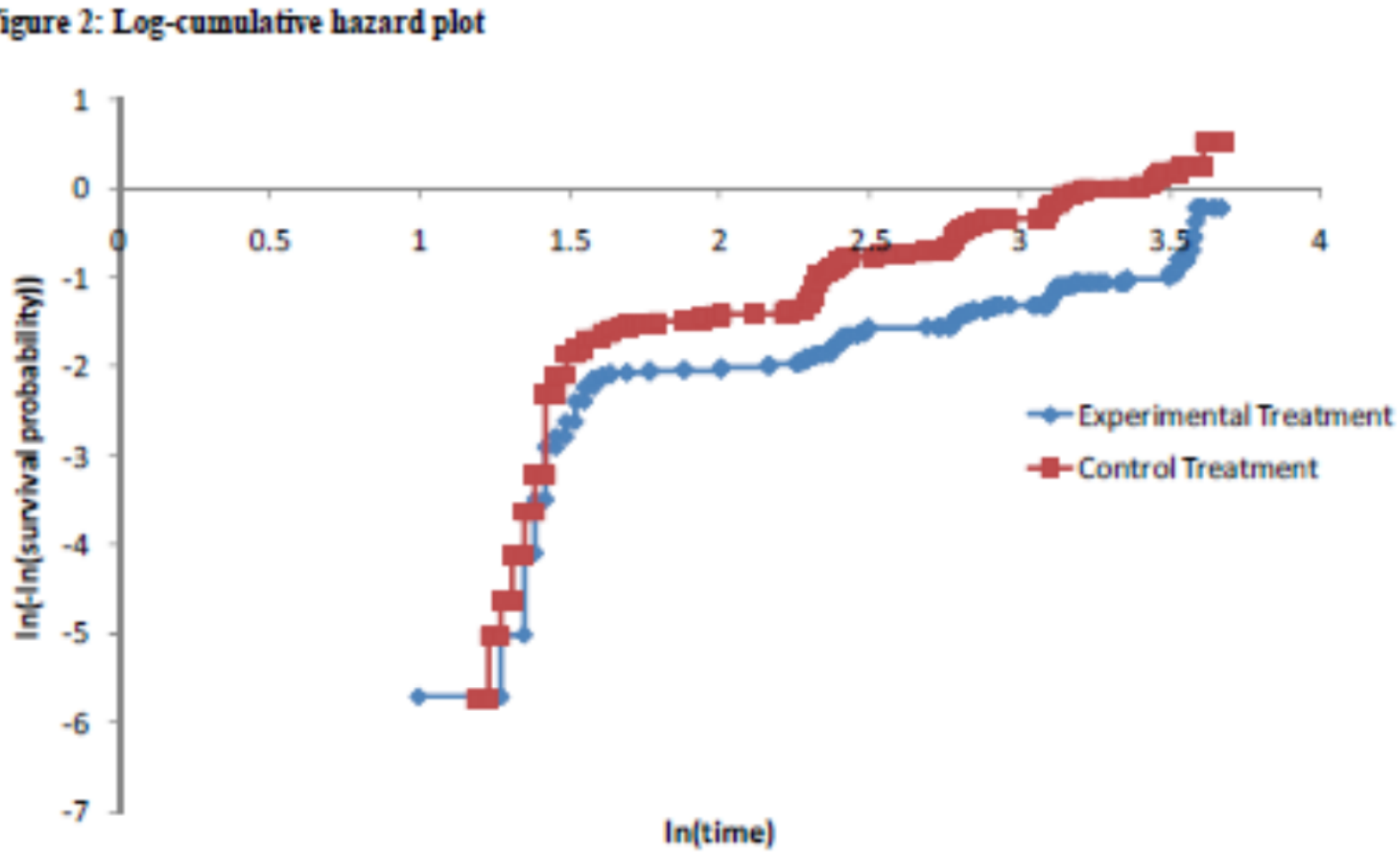


Here, the effect is negative in the early period and positive in the late period

source:https://altis.com.au/a-crash-course-in-survival-analysis-

Assessing the proportionality assumption

The assumption can be assessed number of ways : visually



http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf

Testing the non-zero slope of the Schoenfeld residuals

Fully Parametric models (Accelerated Failure Time 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 !

AFT and covariates

- We can incorporate covariates in a sort of similar way as we would do in a linear regression model $log(T) = \beta_0 + X\beta_1 + \epsilon$

T	$\log(T)$
Exponential	Extreme value
Weibull	Extreme value
Log-logistic	Logistic
Lognormal	Normal

Choosing the "right" distribution

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

Goodness of fit metrics

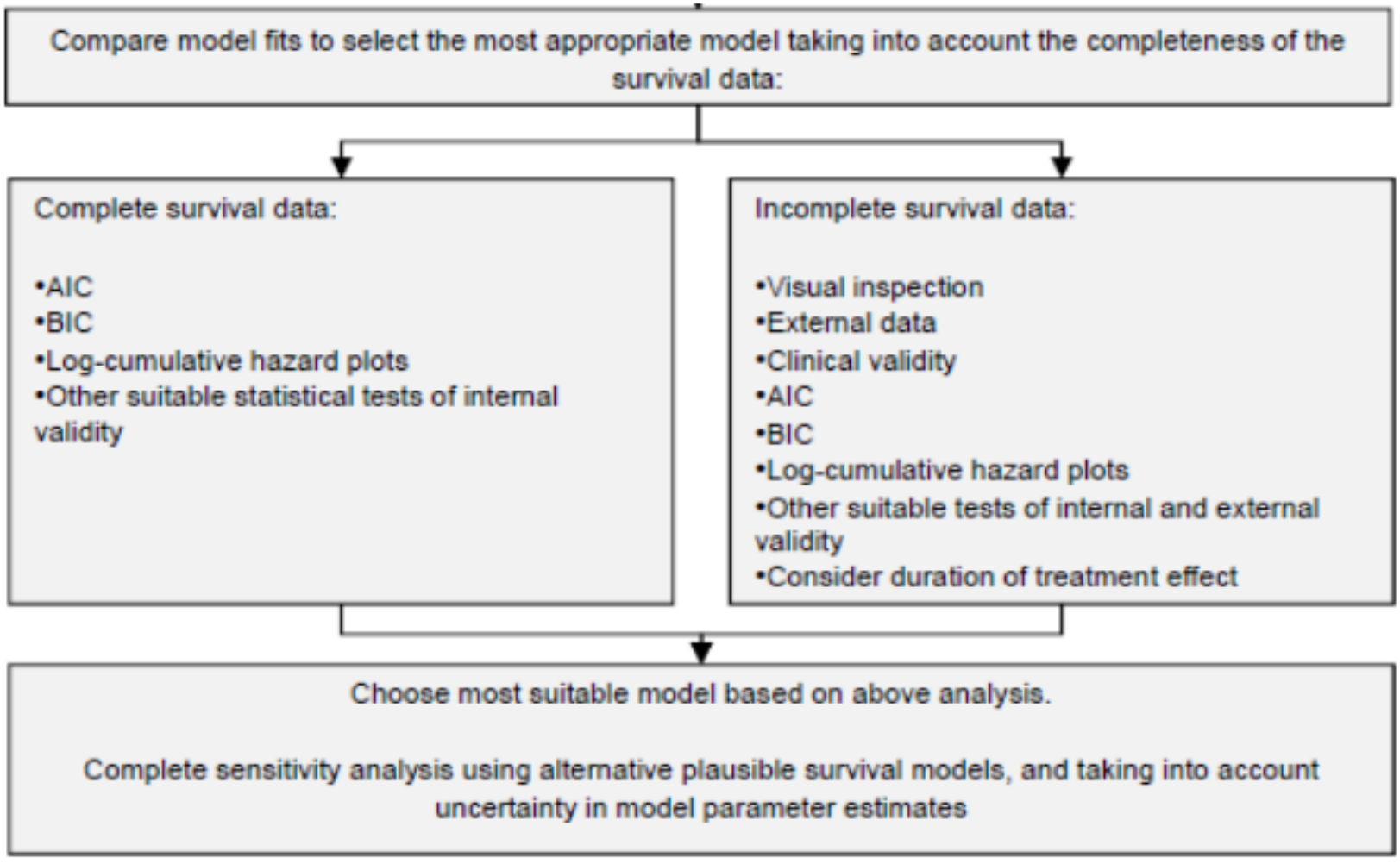
- Likelihood based metrics
- Akaike Information Criterion (AIC)
- Bayesian Information Criterion (BIC)
- Performance based metrics
- Sensitivity , Specificity
- (time dependent) Receiver Operating characteristic (ROC) curve
- Area Under the Curve (AUC)
- c- statistic

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)*

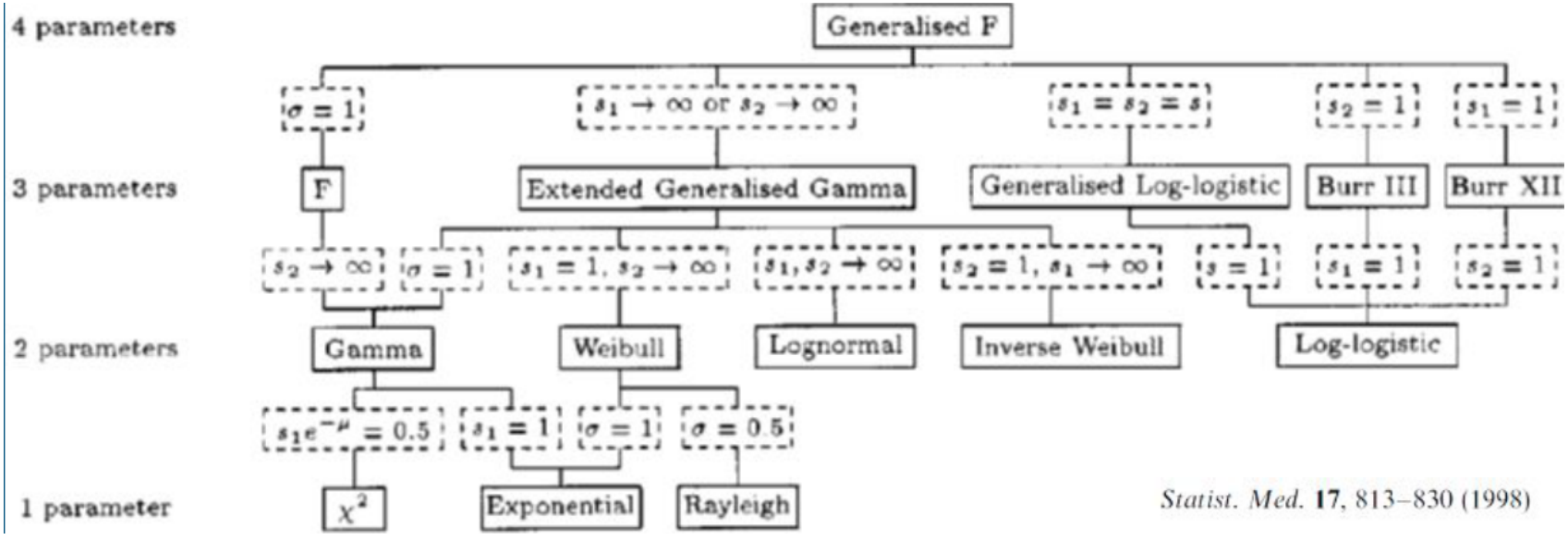
Choosing the "right" distribution

Latimer et al 2011 (DSU 14)



Flexible Survival models

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



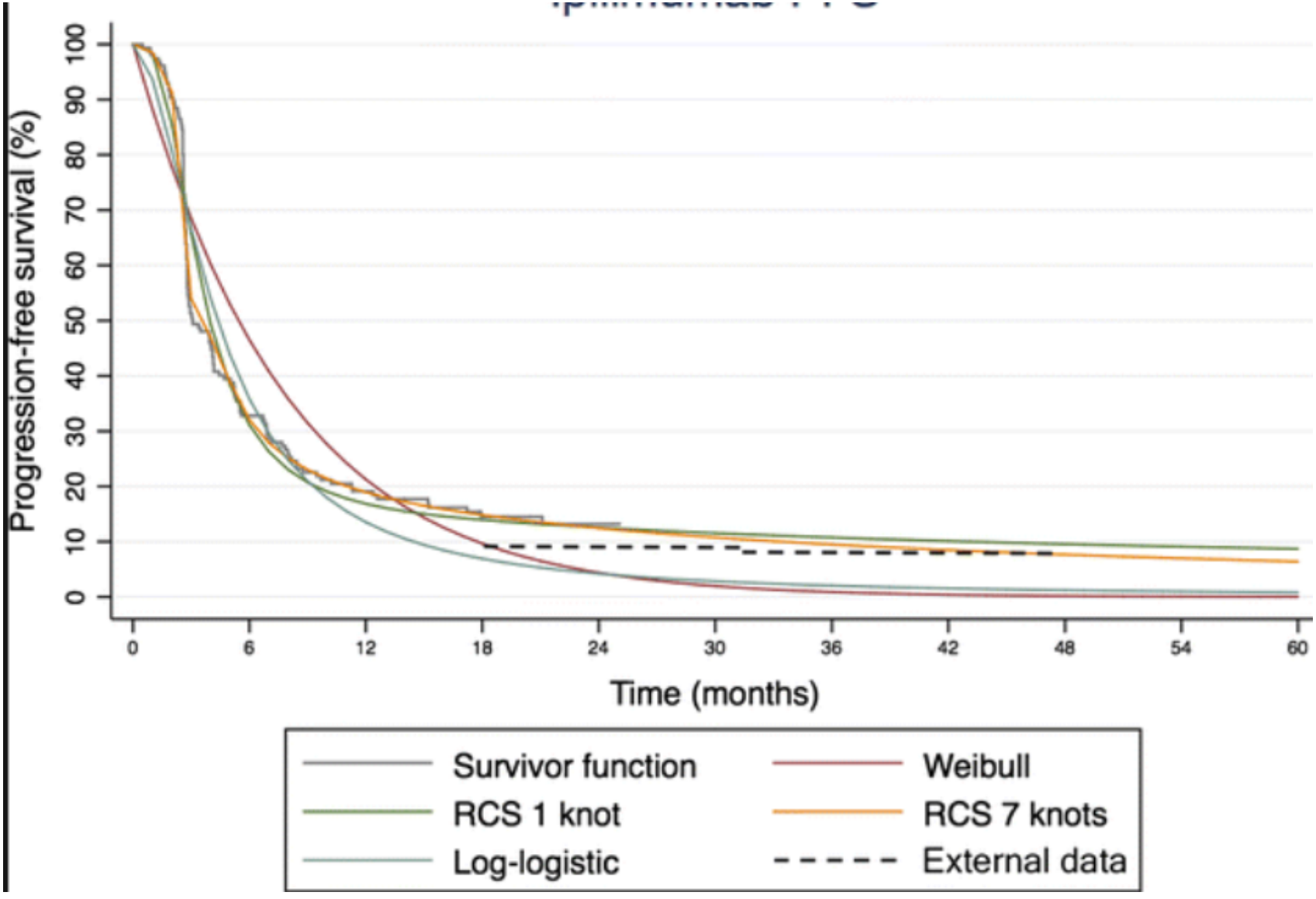
Statist. Med. **17**, 813–830 (1998)

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
- TSD 2020

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 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?
- Regardless of the approach, the implied (observed or predicted) treatment effect should be presented

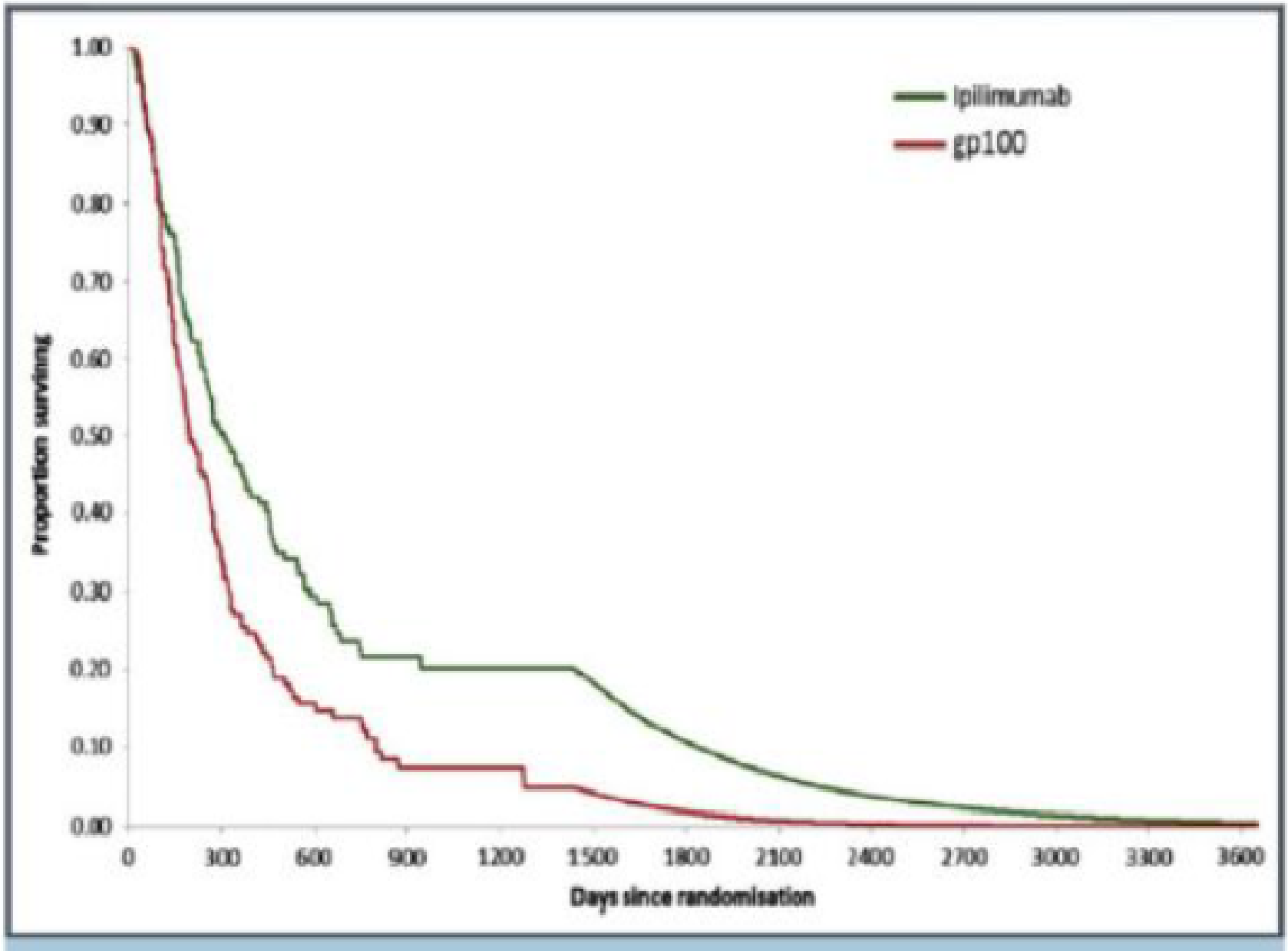
Approaches in extrapolation

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



- Extrapolate using the fitted curve

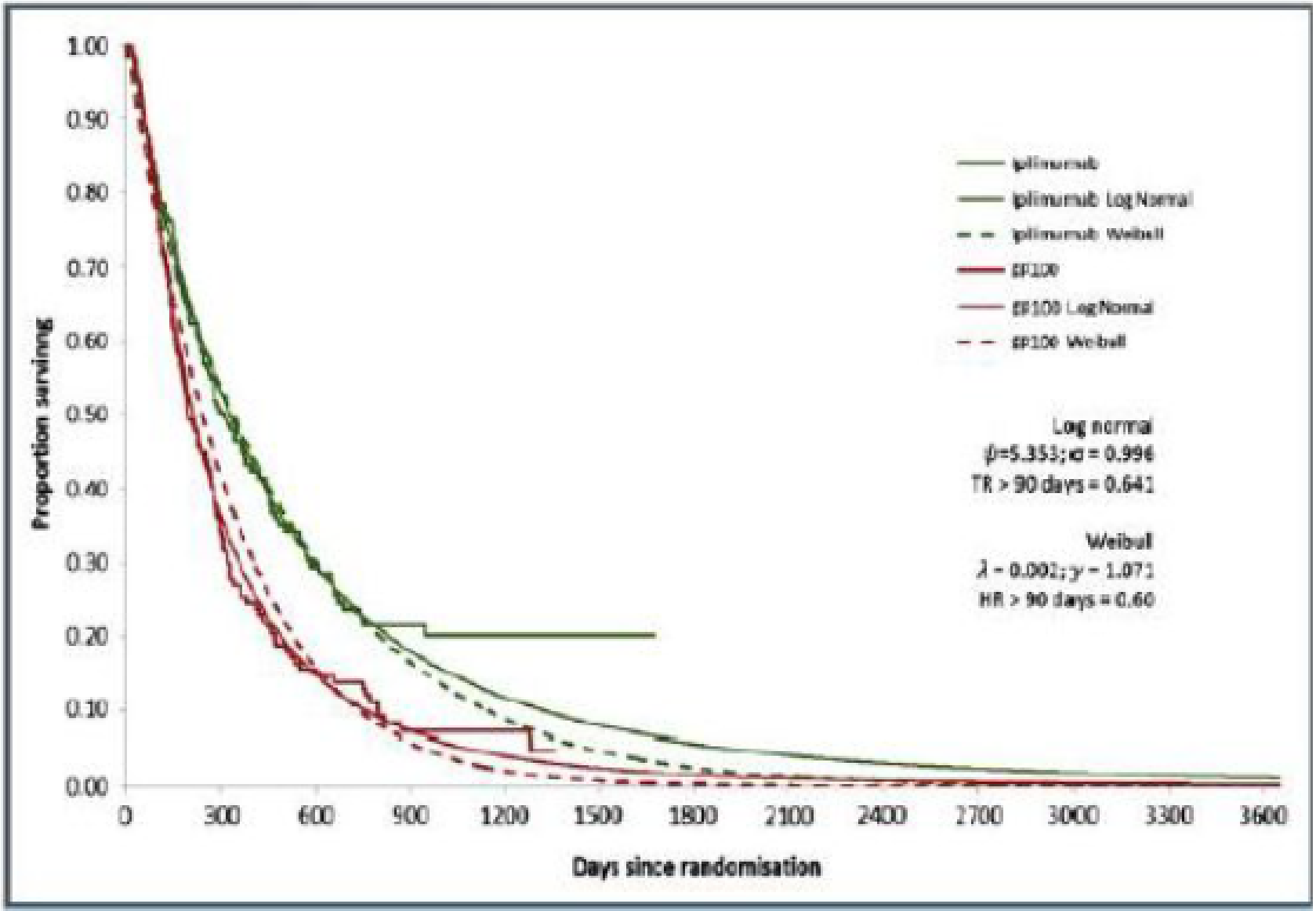
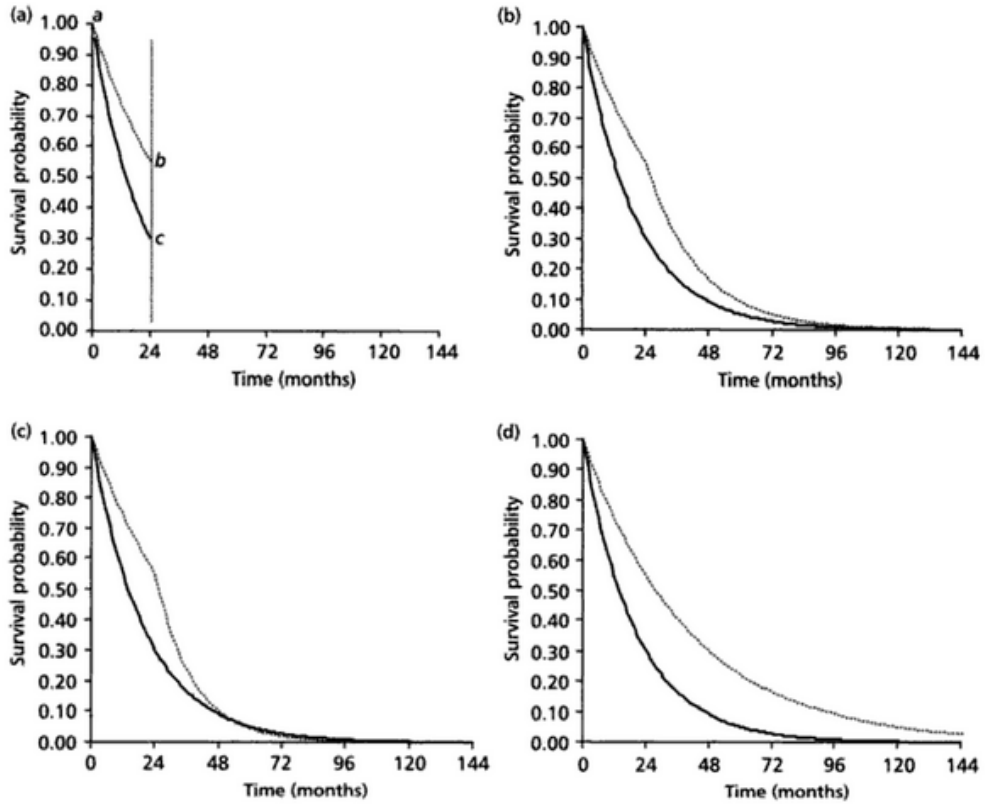


FIGURE 7: Case study showing empiric Kaplan-Meier curves and log-normal survivor functions.

Extrapolating a relative treatment effect

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



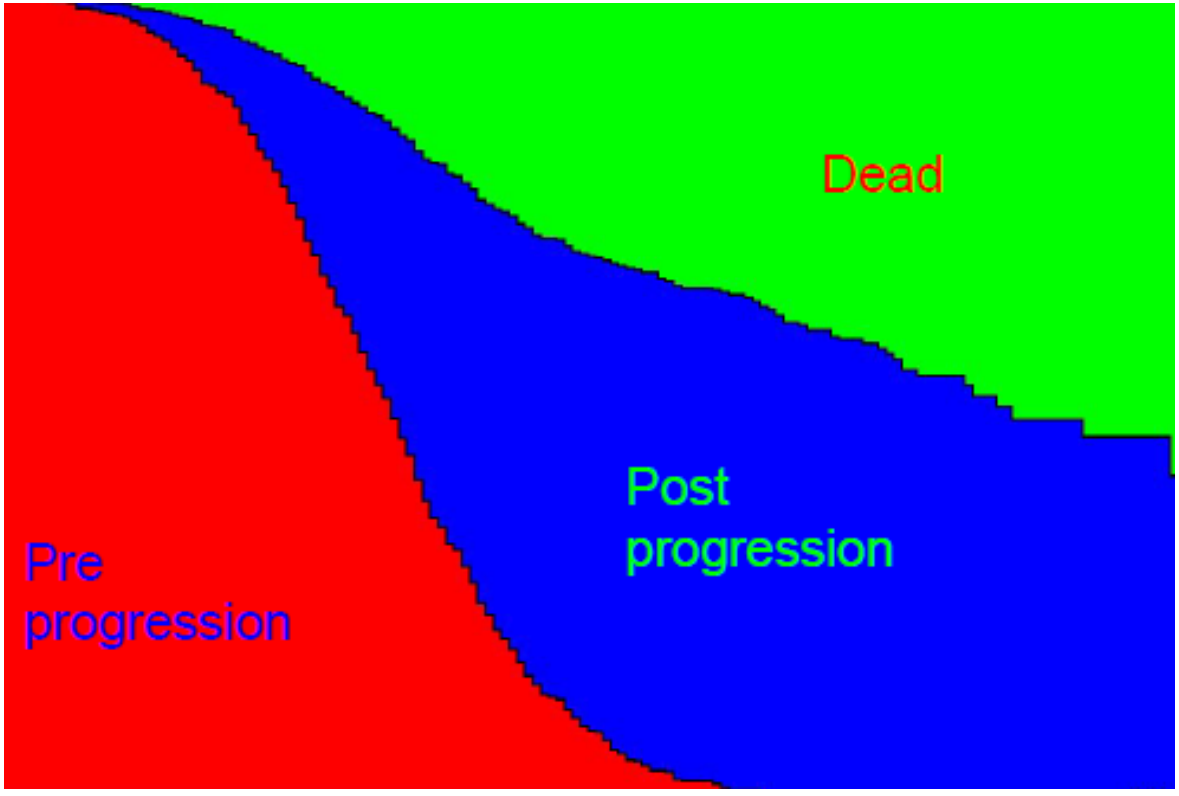
Survival analysis in decision modeling

The DARTH Workgroup

petros.pechlivanoglou@sickkids.ca

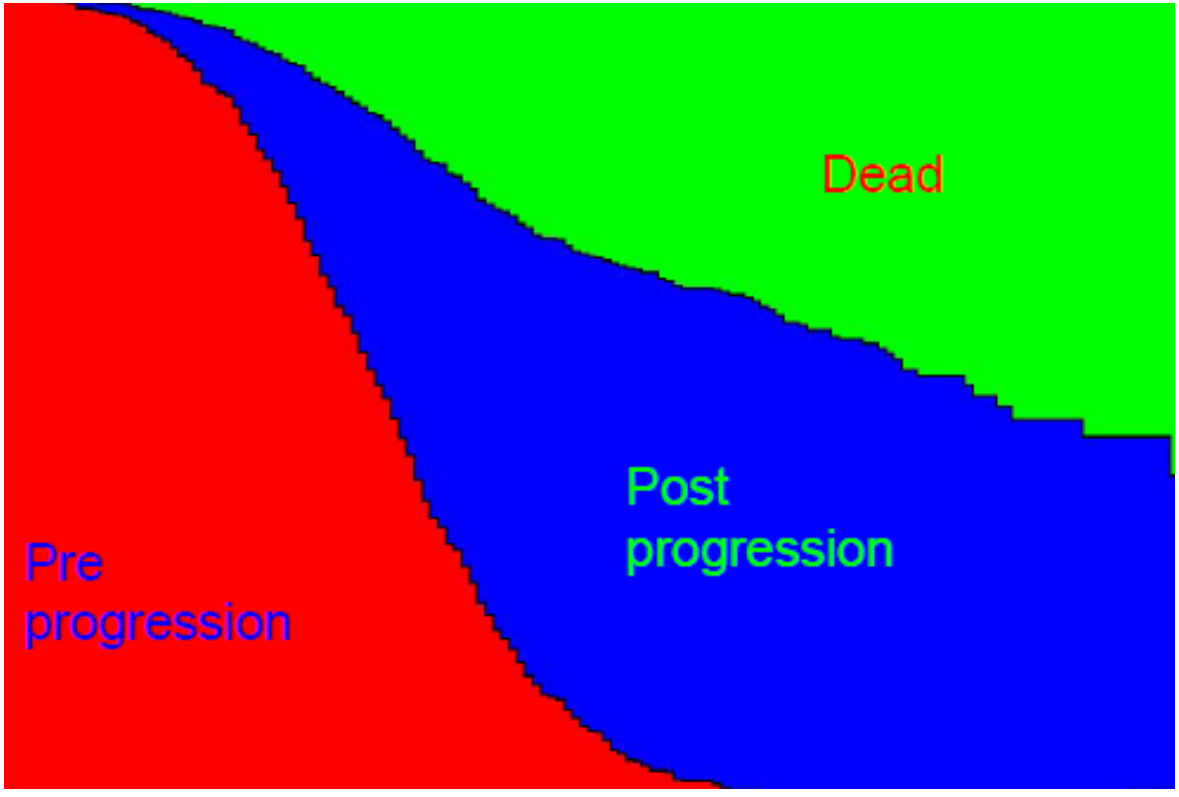
Partitioned survival models

- 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)

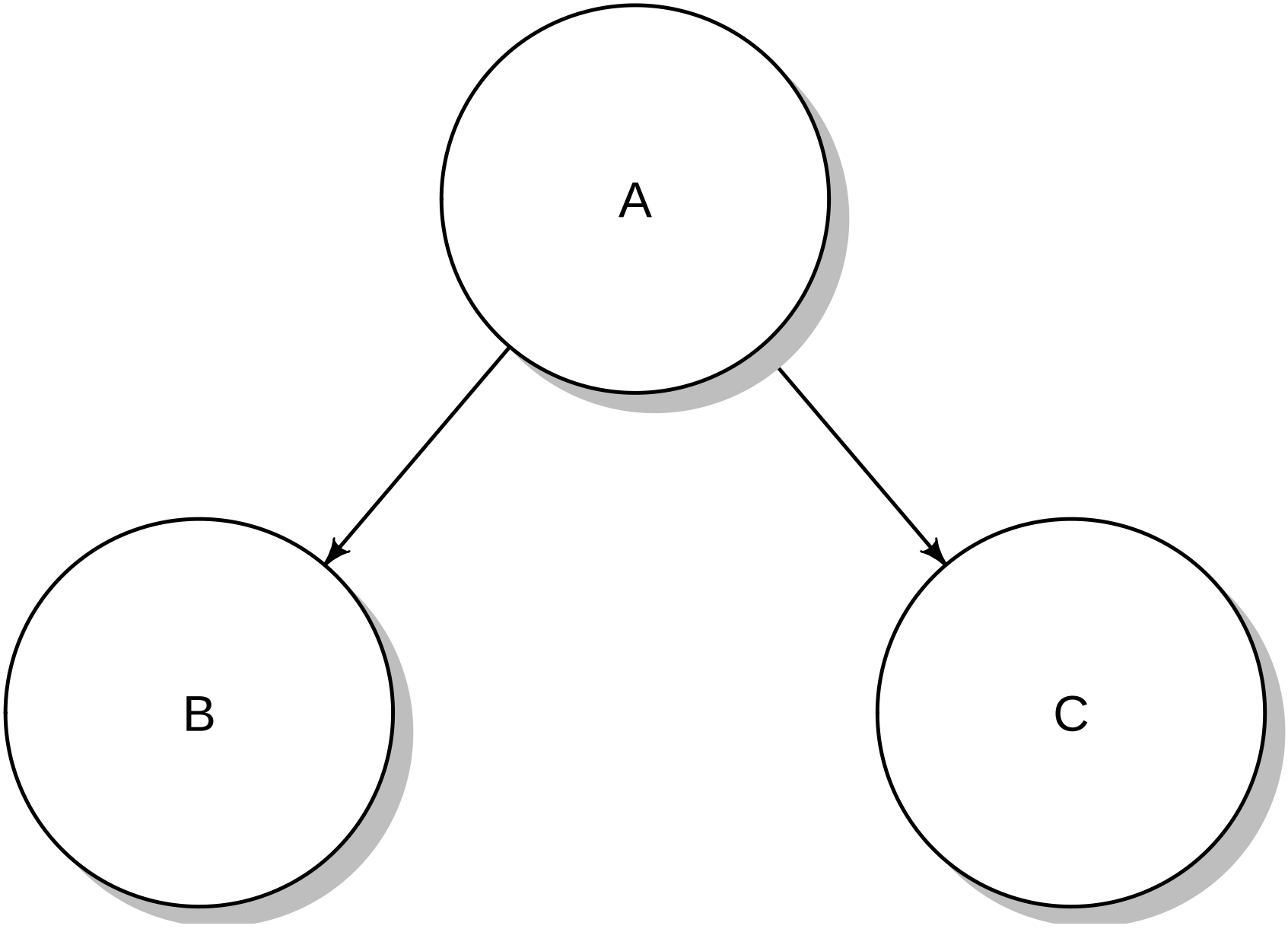
MEDICAL DECISION MAKING/MAY 2017 ORIGINAL ARTICLE

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

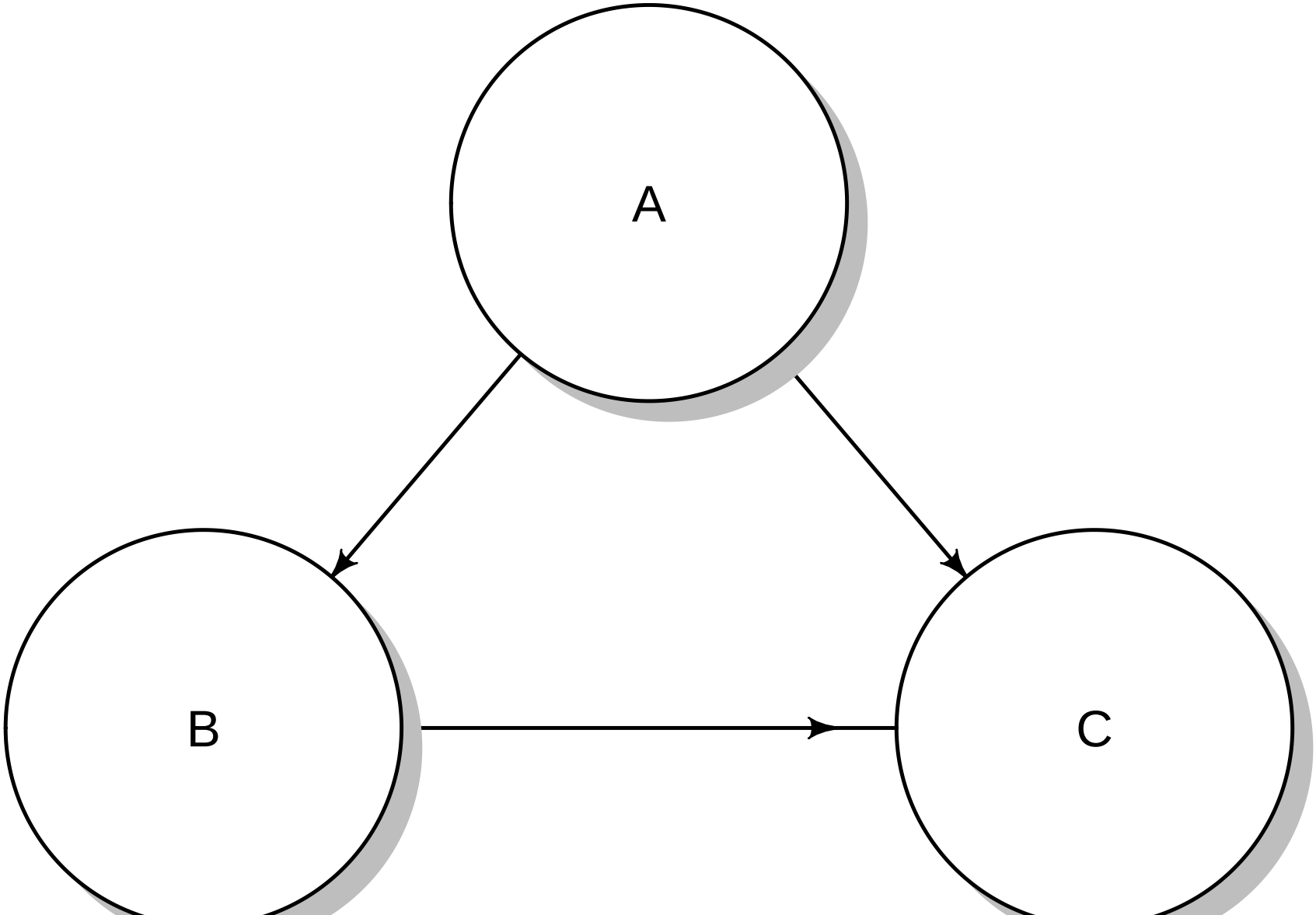
Competing Risks

- 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)