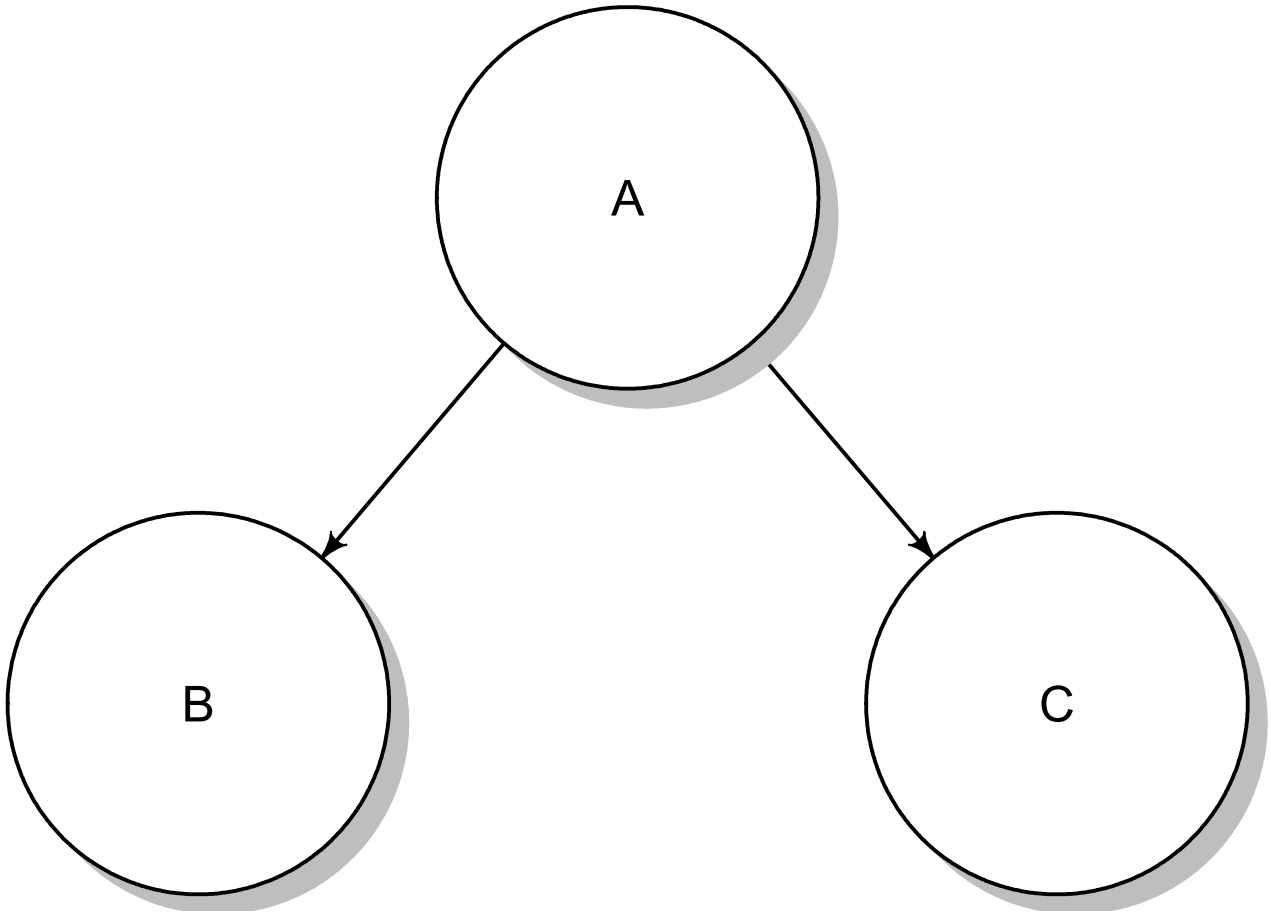
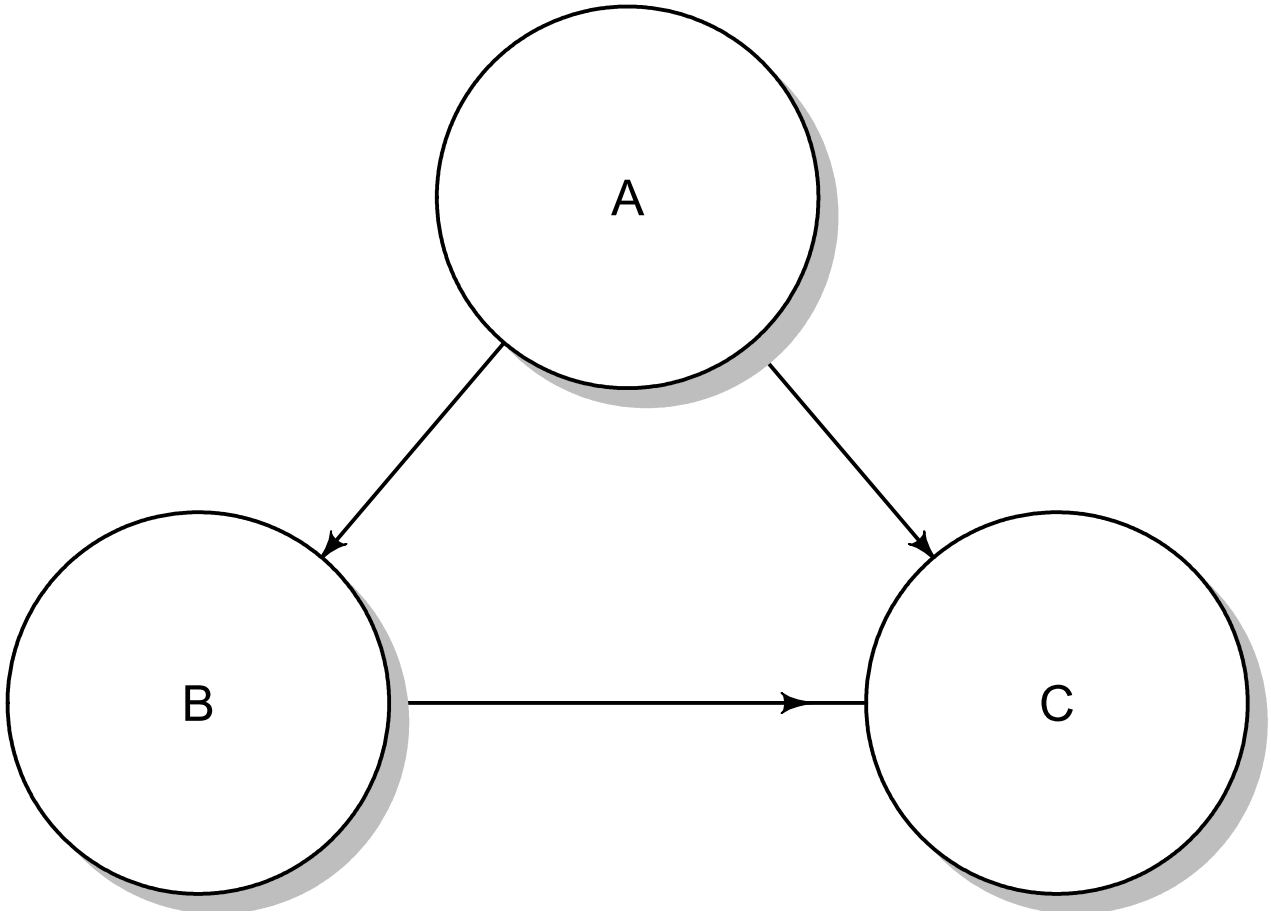
Competing Risks

- 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*

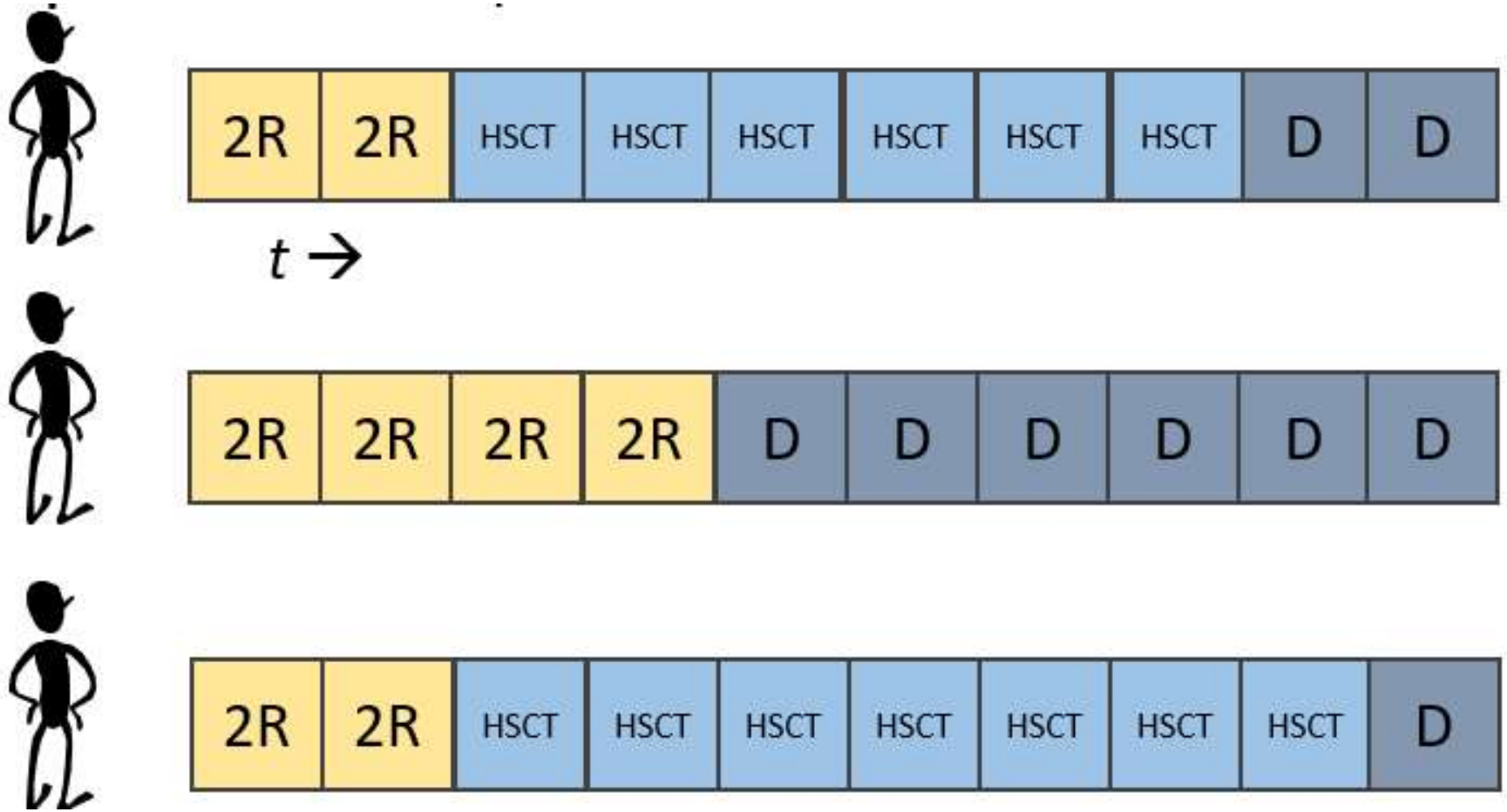
flexsurv: A Platform for Parametric Survival Modeling in R

Christopher H. Jackson
MRC Biostatistics Unit

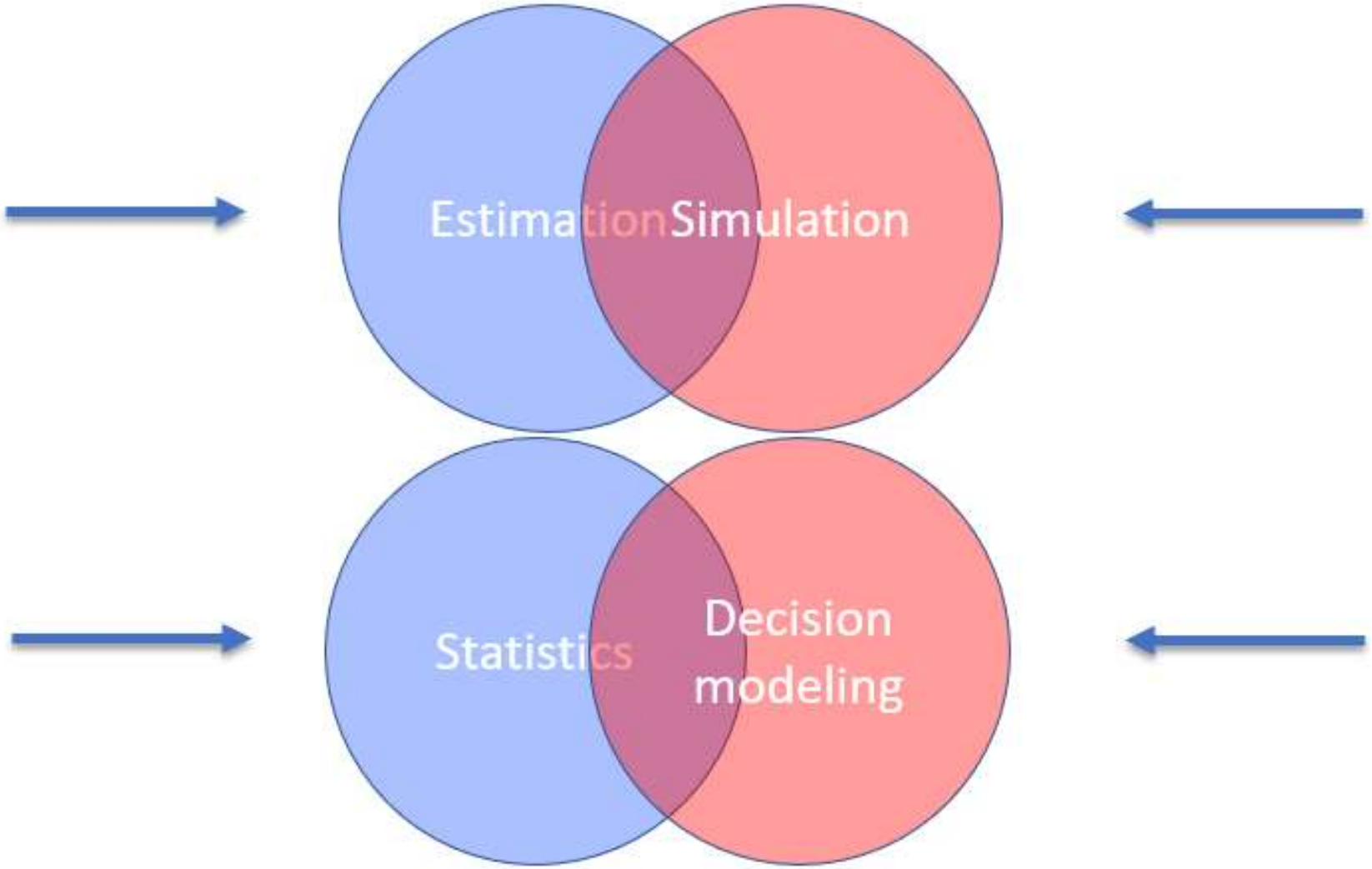
Great resource for both survival fitting and multistate models

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

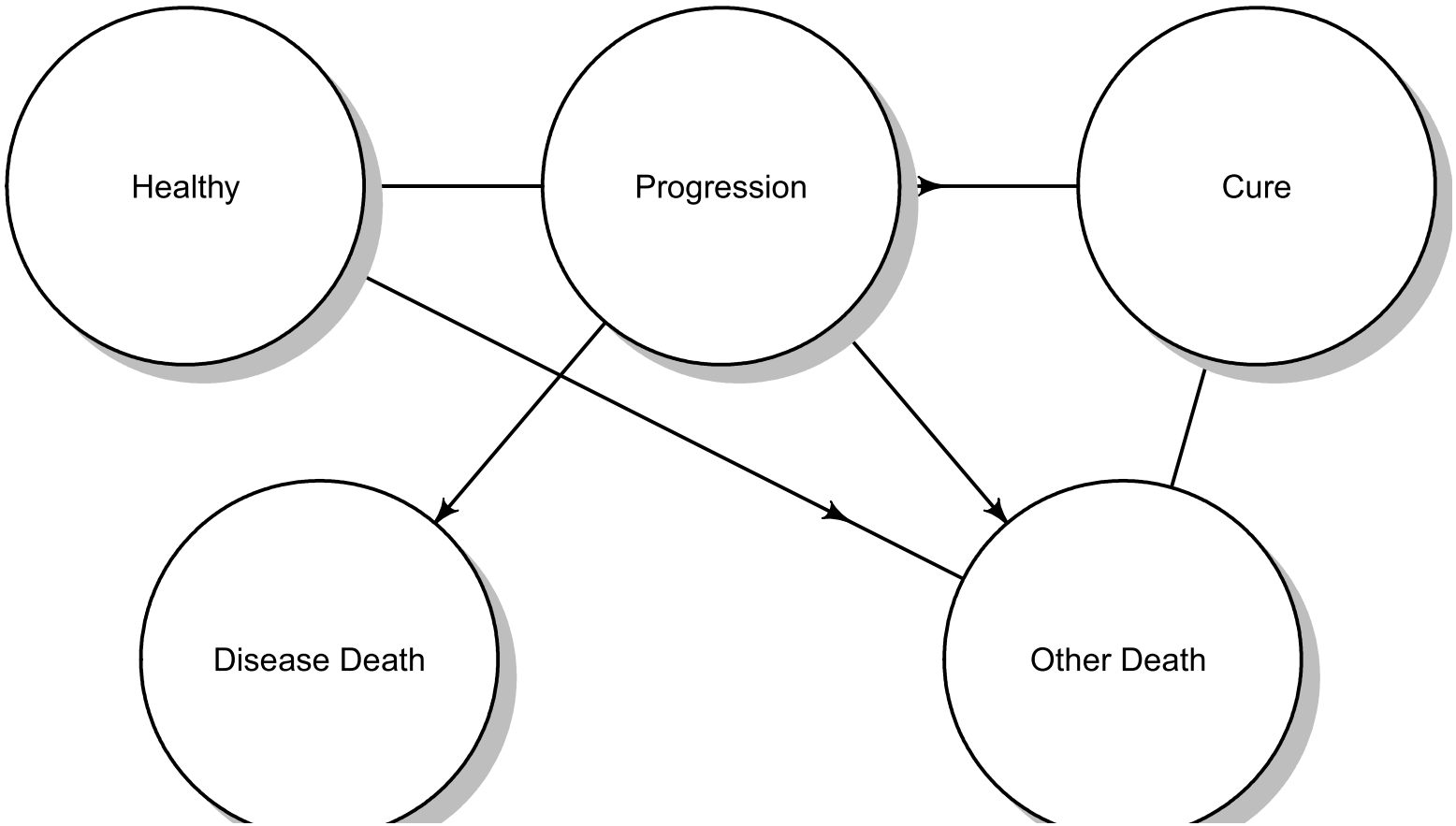
Document name:	Natalizumab in HARRMS_FINAL.doc
Product:	Tysabri® (natalizumab)
Manufacturer:	Biogen Idec
Document written by:	Biogen Idec, Heron Evidence Development
Document customer:	The National Institute for Health and Clinical Excellence (NICE)
Document purpose:	To present the clinical and cost-effectiveness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

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!