A comparison of different joint models for longitudinal and competing risks data

With application to an epilepsy drug randomized control trial

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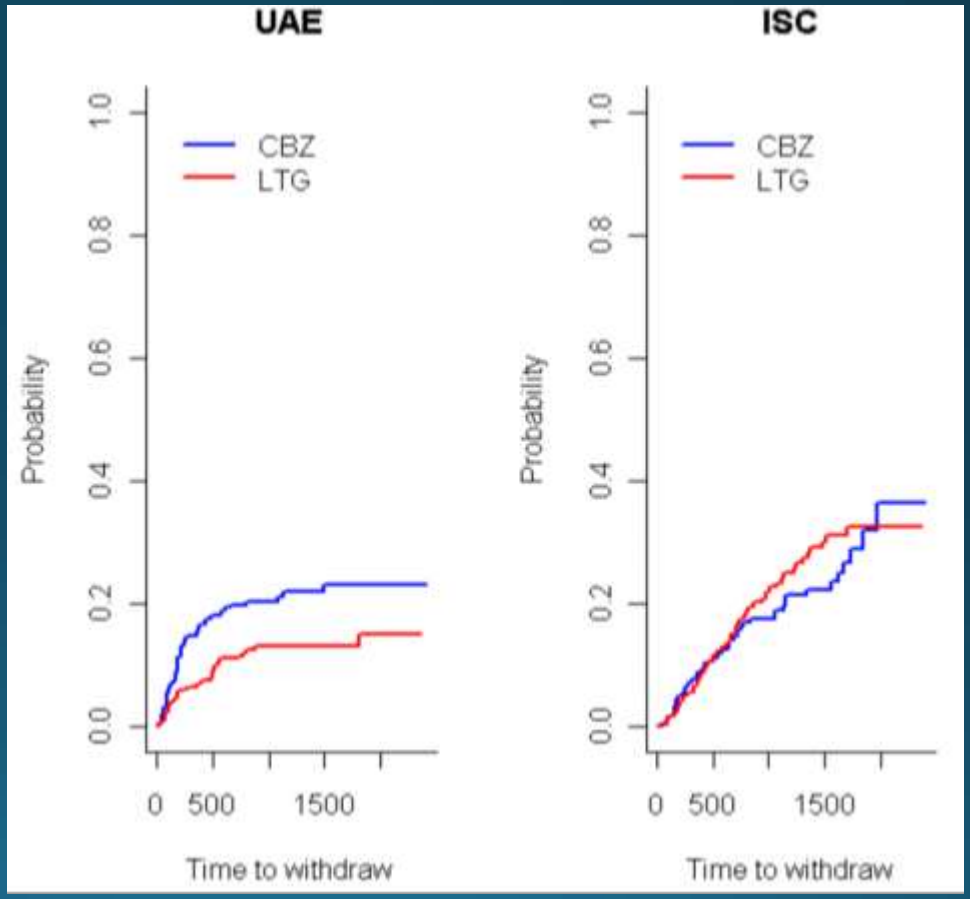
SANAD trial

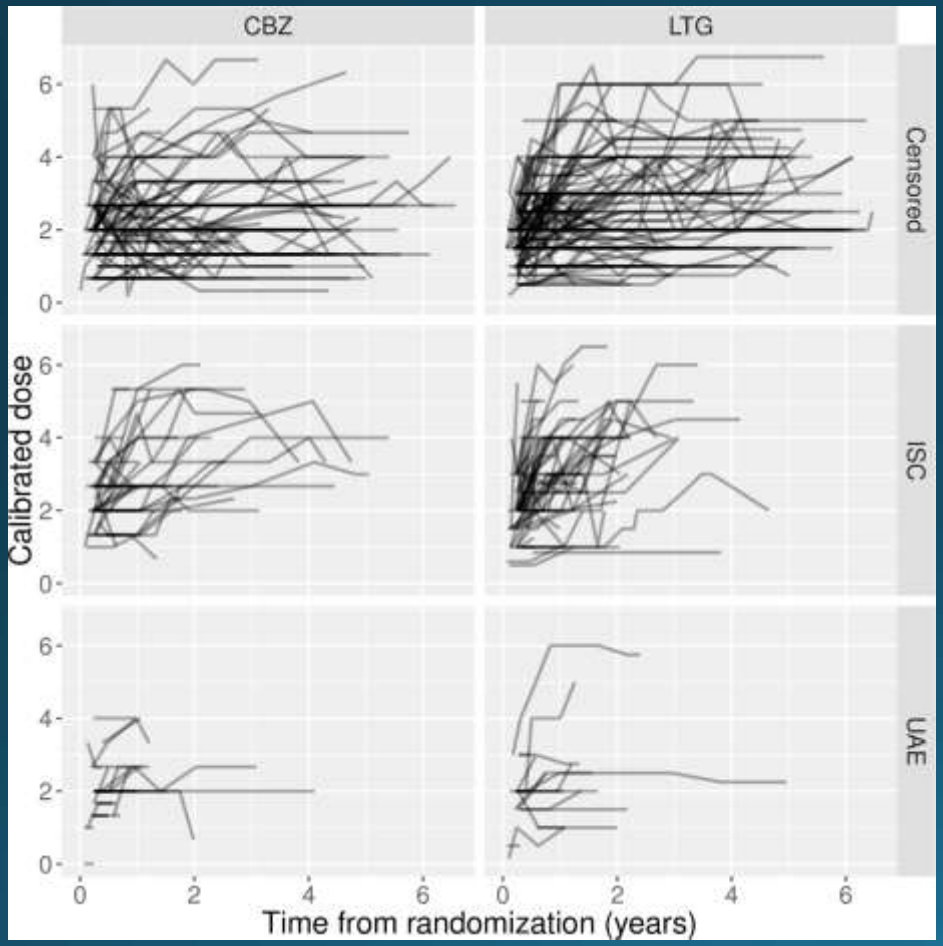
- SANAD (**S**tandard **A**nd **N**ew **A**ntiepileptic **D**rugs) was a non-blinded randomized control trial recruiting patients with epilepsy to test anti-epilepsy drugs (AEDs)
- Patients were randomized to one of 5 drugs
- Subgroup analysis (*n* = 605 patients) comparing 2 drugs: LTG (newer drug) vs. CBZ (standard)
- Primary outcome was time to treatment failure, which could be attributed to either:
  - Inadequate seizure control (ISC)
  - Unacceptable adverse effects (UAE)

Competing risks

- If we consider the time to treatment failure due to a specific cause, we have competing risks data
- Secondary objective: Is LTG superior to CBZ in terms of UAE and ISC?

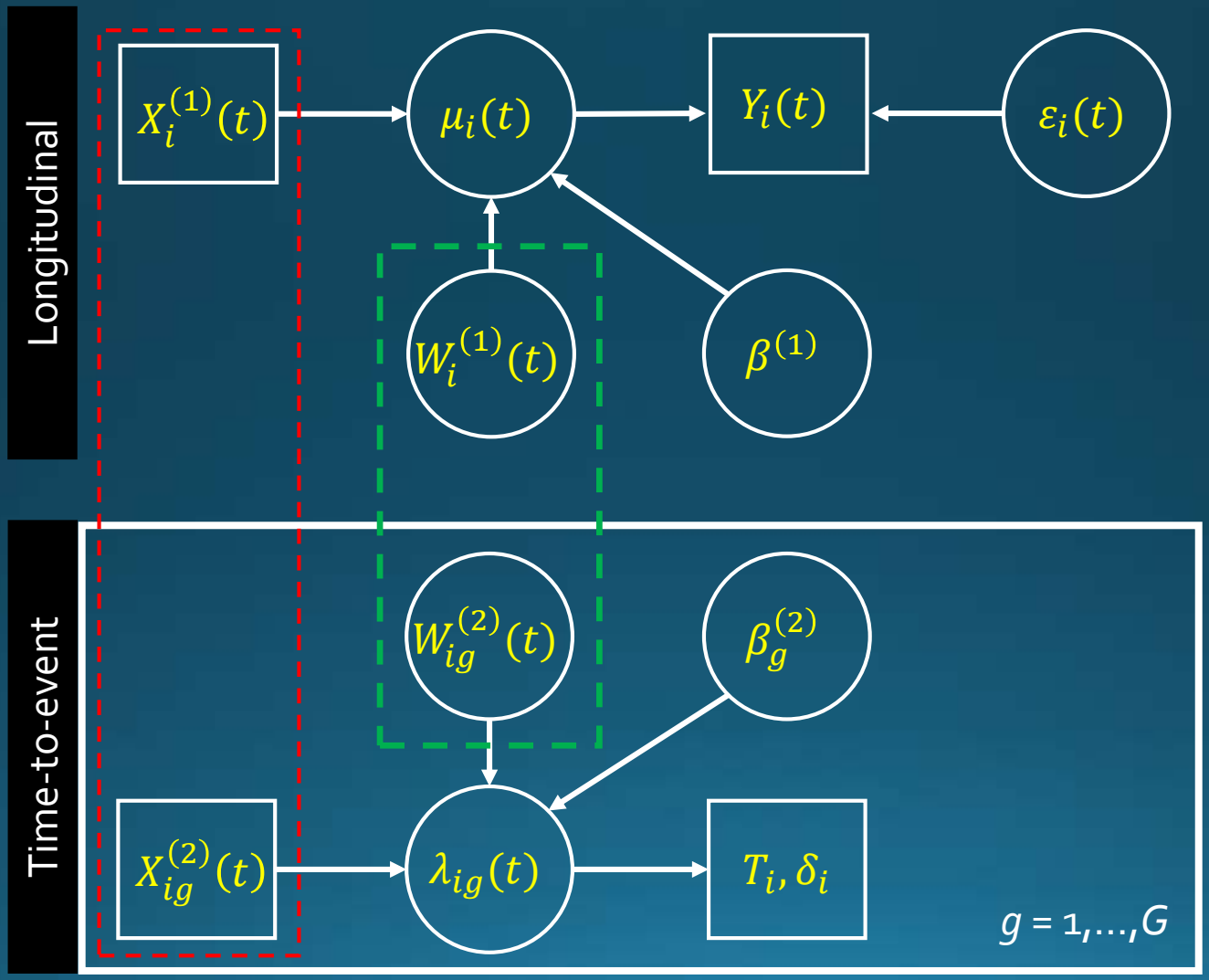


Drug titration



- It was suggested that different titration rates may have been to the disadvantage of standard drug CBZ
- AED titrated more quickly brings benefits in terms of seizure control but be more likely to cause adverse effects

Joint modelling of a longitudinal outcome and competing risks: *a general formulation*



Joint modelling

- For subject i $(= 1, \ldots, n)$ with observation times $t_{ij} = 1, \ldots, n_i$, with $X_i = 1$ (LTG) or $= 0$ (CBZ)

- **Longitudinal sub-model** (drug titration):
  - $y_i(t_{ij}) = \mu_i(t_{ij}) + \varepsilon_{ij}$
  - $\mu_i(t_{ij}) = \beta_0^{(1)} + \beta_1^{(1)} t_{ij} + \beta_2^{(1)} X_i + \beta_3^{(1)} X_i t_{ij} + W_i^{(1)}(t_{ij})$
    $= \beta_0^{(1)} + \beta_1^{(1)} t_{ij} + \beta_2^{(1)} X_i + \beta_3^{(1)} X_i t_{ij} + b_{i0} + b_{i1} t_{ij}$
  - $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$
  - $(b_{i0}, b_{i1})^T \sim N_2(0, \Sigma)$

- **Time-to-event sub-model** (treatment failure due to competing risks):
  - $\lambda_{ig}(t) = \lambda_{0g}(t) \exp\left\{X_i \beta_g^{(2)} + W_{ig}^{(2)}(t)\right\}$

Models evaluated

Model	Reference
1	Williamson PR et al. Joint modelling of longitudinal and competing risks data. *Stat Med*. 2008;27: 6426–6438.
2	Elashoff RM et al. A joint model for longitudinal measurements and survival data in the presence of multiple failure types. *Biometrics*. 2008;64: 762–771.
3	Rizopoulos D. *Joint Models for Longitudinal and Time-to-Event Data, with Applications in R*. Boca Raton, FL: Chapman & Hall/CRC; 2012.
4	Andrinopoulou E-R et al. Joint modeling of two longitudinal outcomes and competing risk data. *Stat Med*. 2014;33: 3167–3178.
5	Proust-Lima C et al. Joint modelling of repeated multivariate cognitive measures and competing risks of dementia and death: a latent process and latent class approach. *Stat Med*. 2015; In press.

Only ones with code / software packages available

Primary model differences:
Distribution, software, estimation algorithm

Model	Baseline hazards	Software	Estimation algorithm
1	Non-parametric (unspecified)	R code	MLE (EM algorithm) + bootstrap for SE / CIs
2	Non-parametric (unspecified)	C code	MLE (EM algorithm)
3	B-spline basis (on log-hazard scale)	R package (JM)	MLE (EM + Newton-Raphson algorithms)
4	Piecewise constant	WinBUGS	Bayesian MCMC
5a	Weibull	R package (lcmm)	MLE (Marquardt algorithm)
5b	Piecewise constant		
5c	Cubic M-splines		

Primary model differences:
Latent association structure

Model	Type	$W_{ig}^{(2)}(t)$
1	Current value of latent process parameterization	$\alpha_g W_i^{(1)}(t)$
2	Random effects parameterization	$\alpha_g \theta_i$ with $\alpha_1 = 1$, $\mathrm{Cov}(b_i, \theta_i) = \Sigma_{b\theta}$ and $\mathrm{Var}(\theta) = \sigma_\theta^2$
3a	Current value parameterization	$\alpha_g \mu_i(t)$
3b	Time-dependent slopes parameterization	$\alpha_g^{(1)} \mu_i(t) + \alpha_g^{(2)} \frac{d}{dt} \mu_i(t)$
3c	Lagged-effects parameterization	$\alpha_g \mu_i(\max\{t - c, 0\})$
3d	Cumulative effects parameterization	$\alpha_g \int_0^t \mu_i(s)\, ds$
3e	Weighted-cumulative effects parameterization	$\alpha_g \int_0^t w(t-s)\mu_i(s)\, ds$
3f	Special case of the random effects parameterization (with fixed component)	$\alpha_g \left(\beta_1^{(1)} + b_{i1}\right)$
4	Random effects parameterization (with fixed component)	$\alpha_g^\top (\tilde{\beta}^{(1)} + b_i)$
5	Association between sub-models accounted entirely for by latent classes	N/A

Primary model differences:
Model 5 as a special case

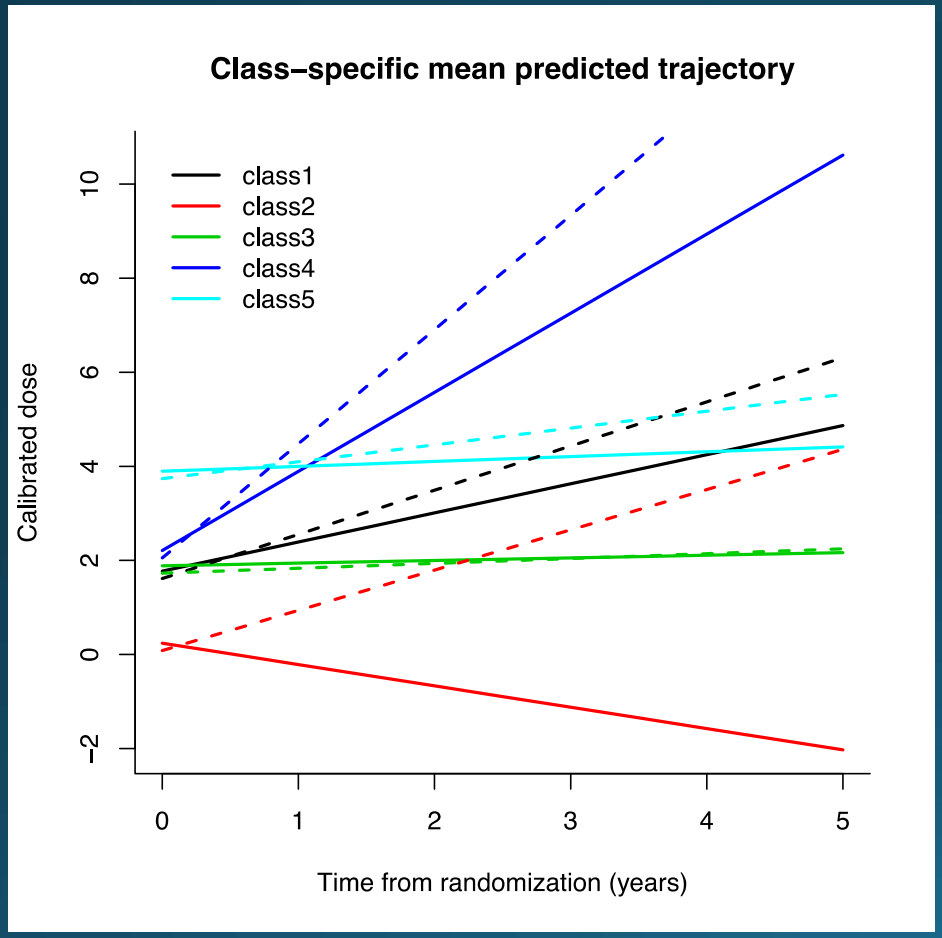
- Association is not captured by specification of $W_{ig}^{(2)}(t)$
- **Basic idea**: assumes each subject i belongs to a single latent class, $a_i \in \{1, 2, \dots, R\}$, and consider covariates (+ coefficients) as being global- or class-specific
- Re-write the sub-models conditional on class, $\mu_i(t_{ij} \mid a_i)$ and $\lambda_{ig}(t \mid a_i)$, and specify a distribution over the classes
- Choose R (=5 in SANAD example) by fitting range of models, and choose one that minimizes BIC statistic

Results

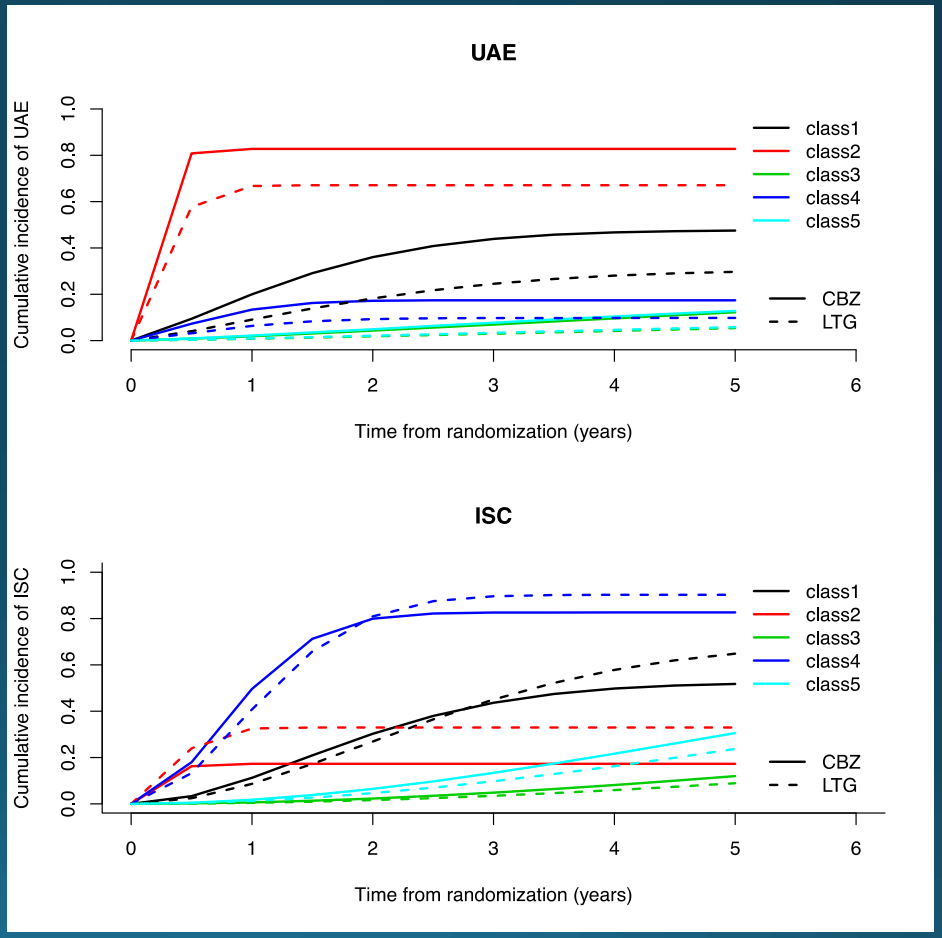
Model	$\beta_1^{(2)}$ [ISC] (95% CI)	α_1 [ISC] (95% CI)	$\beta_2^{(2)}$ [UAE] (95% CI)	α_2 [UAE] (95% CI)	Computation time
Separate	0.015 (-0.344, 0.374)	NA NA	**-0.608** (-1.102, -0.192)	NA NA	<1s
1	0.028 (-0.329, 0.366)	**0.590** (0.425, 0.768)	**-0.660** (-1.090, -0.221)	**-0.925** (-1.378, -0.519)	17s [MLEs] 45m [SEs]
2	-0.306 (-0.744, 0.131)	**-1.502** (-1.941, -1.062)	**-0.543** (-0.997, -0.089)	1.000 Reference	5h 22m
3a	-0.119 (-0.482, 0.244)	**0.598** (0.448, 0.747)	**-0.625** (-1.044, -0.207)	**-0.926** (-1.246, -0.607)	54s
3b	**-0.592** (-1.036, -0.148)	0.120 [CV] (-0.138, 0.377) **2.334** [Slope] (1.360, 3.308)	**-1.212** (-1.832, -0.593)	**-1.239** [CV] (-1.642, -0.836) **2.724** [Slope] (1.002, 4.447)	52s
3c	-0.055 (-0.417, 0.306)	**0.591** (0.426, 0.756)	**-0.696** (-1.118, -0.274)	**-1.016** (-1.347, -0.684)	52s
3d	-0.035 (-0.395, 0.326)	**0.212** (0.133, 0.291)	**-0.612** (-1.027, -0.196)	-0.156 (-0.381, 0.070)	56s
3e	-0.074 (-0.436, 0.288)	**1.495** (1.095, 1.895)	**-0.613** (-1.029, -0.196)	-0.869 (-1.848, 0.110)	51s
3f	-0.090 (-0.497, 0.317)	**2.619** (2.027, 3.212)	**-0.868** (-1.446, -0.290)	**-8.558** (-10.143, -6.972)	53s
4	-0.211 (-0.680, 0.254)	-0.213 [Intercept] (-0.554, 0.088) **2.937** [Slope] (2.200, 3.854)	**-0.815** (-1.341, -0.307)	**-1.420** [Intercept] (-1.889, -0.972) **1.713** [Slope] (0.052, 2.998)	26h 22m
5a	-0.366 (-0.866, 0.134)	NA	**-0.876** (-1.391, -0.360)	NA	3m 34s
5b	-0.142 (-0.597, 0.314)	NA	**-0.693** (-1.178, -0.207)	NA	2m 50s
5c	NA	NA	NA	NA	NA

Results: *Model 5a*

Longitudinal sub-model



Competing risks sub-model



Patients distributed 22.8%, 6.6%, 58.3%, 7.4%, and 4.8% for classes 1 to 5, respectively

Model pros & cons

Model	Software	Speed	Other
1	• Currently, only code available – not yet in an R package	• SEs estimated by bootstrap can be slow	• Extends the seminal model by Henderson et al. (2000)
2	• Currently only available as C code files – not standard software choice of biostatisticians	• Slow to converge	• Constraints on latent association structure complicates interpretation
3	• Available as a comprehensive joint model package in R	• Very fast	• Flexible range of latent association structures • Fits a contrasts model; i.e. estimates ψ and ϕ such that $\beta_2^{(2)} = \beta_1^{(2)} + \psi$ and $\alpha_2 = \alpha_1 + \phi$, respectively
4	• Code and data requires substantial manipulation – need to be fluent in BUGS language	• WinBUGS is slow to converge + poor mixing	• Model was originally developed for multivariate longitudinal data (incl. ordinal outcomes)
5	• Available as a comprehensive joint model package in R	• Need to fit multiple models with different number of classes – moderately slow • Need to fit final model from multiple initial values to ensure reached global maximum – slow	• Flexible choice of survival models • Can't quantify the association between two sub-models • Don't need to worry about correctly specifying form of $W_{ig}^{(2)}(t)$

Conclusions on joint models

- Methodological research into joint models of longitudinal and competing risks data is growing
- Software for fitting models is limited
- Limited model fit statistics, diagnostics, and predictive assessment tools
- Limited guidance on model choice and association structure

More work required before integration into routine biostatistical analyses can be realized

Questions?

Code and data available from
https://github.com/graemeleehickey/comprisk

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UoL joint model research group: goo.gl/k7BpBq

R package `joineR` soon to be updated with competing risks code