Joint modelling of longitudinal biomarkers for survival prediction: an application using clinical trial data

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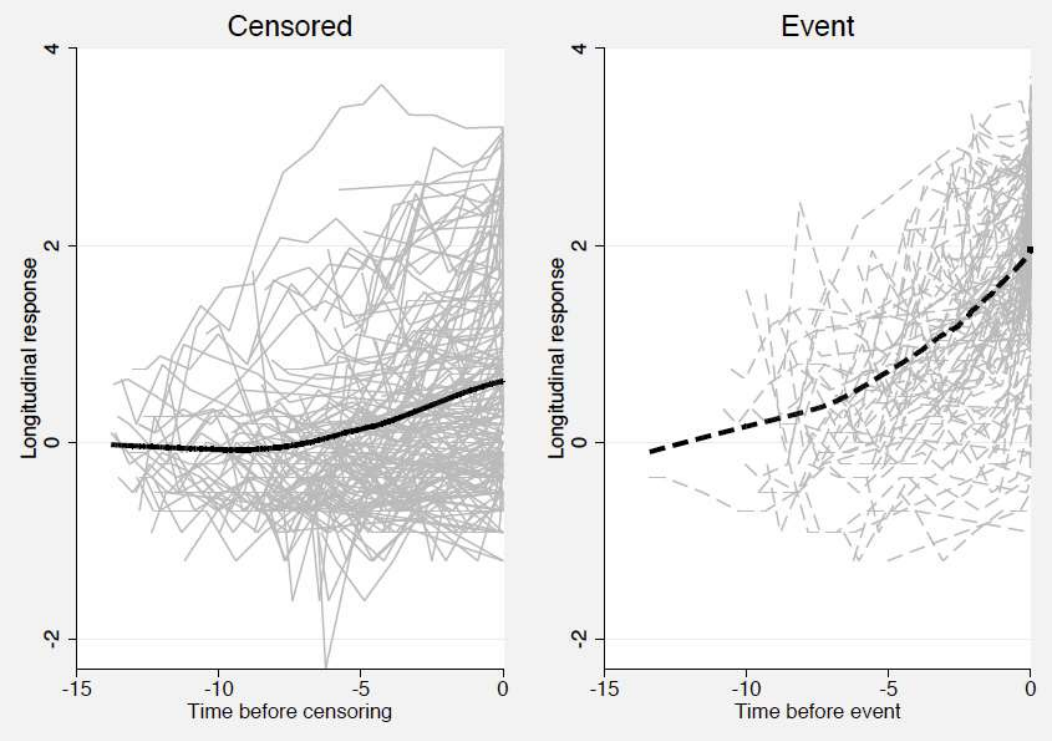
Joint Modelling: Introduction

- In clinical studies we are often interested in the association between a **longitudinal biomarker** and a **time-to-event outcome**, to:
  - Estimate the biomarker profile over time - drop out due to death represents **informative dropout** - need to adjust for this
  - **Predict** the time-to-event outcome for censored patients, using data on the biomarker profile up to a specific time point
- We can achieve both of these aims by using a **joint model**



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Joint Modelling: Introduction

Survival submodel

e.g. proportional hazards/parametric model

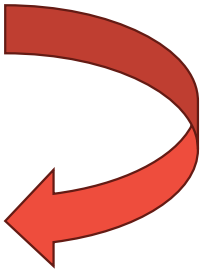
hazard(t) = Survival function + Error

Longitudinal submodel

Assume we observe a continuous biomarker (y) over time

y(t) = Trajectory function + Error

(estimated value of the biomarker for patient i at time t)



Joint model

hazard(t) = Survival function + α Trajectory function + Error

α is called the association parameter, and is the log Hazard Ratio (HR) for mortality per 1-unit increase in the value of the biomarker

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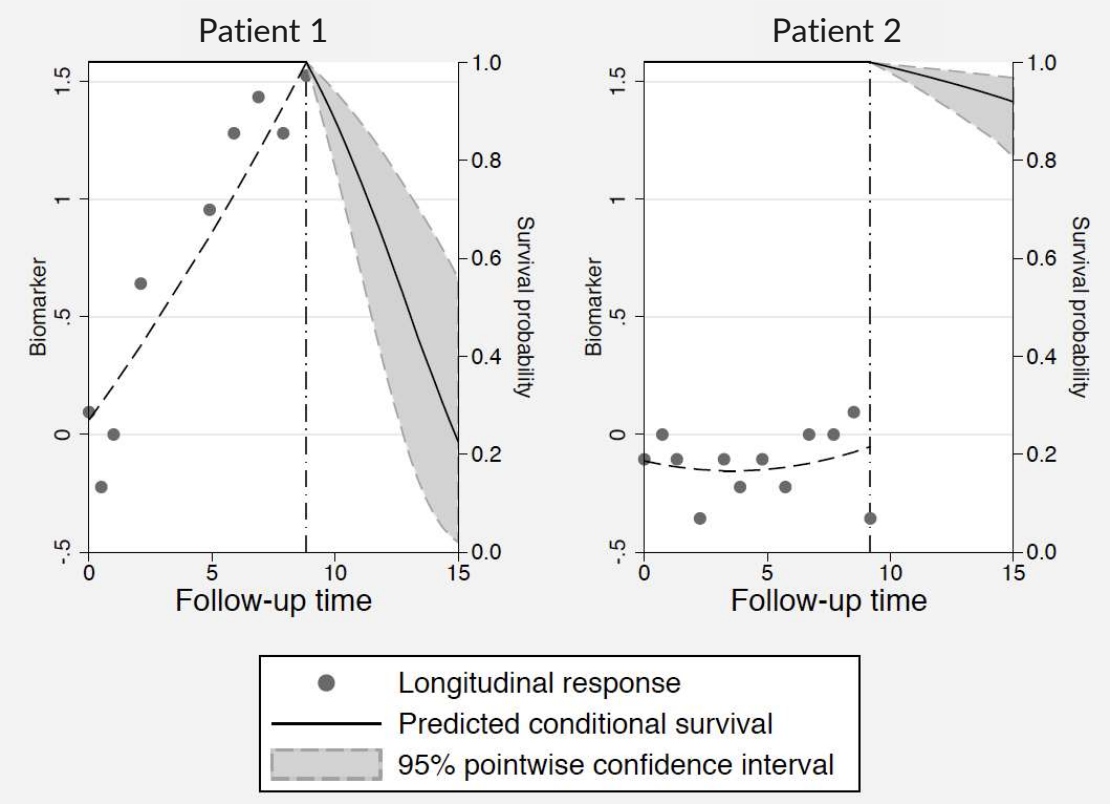
Joint Modelling: Introduction

Having estimated a joint model, we can:

- Make **survival predictions** for individual patients based on their biomarker profiles up to a specific time point
- Use these patient-specific predictions to **extrapolate** the study results into the future



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Clinical trial data

- We used an **integrated dataset of 3 early phase trials** (*data-cut 20 July 2021*) which investigated the performance of larotrectinib as a targeted cancer therapy[1]:
  - Phase I adult dose-escalation study [20288]
  - Phase II adolescent & adult basket trial [NAVIGATE]
  - Phase I/II paediatric trial [SCOUT]

- Larotrectinib is an EMA and FDA approved treatment for patients with solid tumours and positive for a *NTRK* gene fusion.

- Early results have shown that larotrectinib is effective at shrinking tumours and preventing progression across a range of tumour types.

- **196 patients** receiving treatment were included in the analysis.

- There were **25 different tumour types** with varying rates of overall survival.

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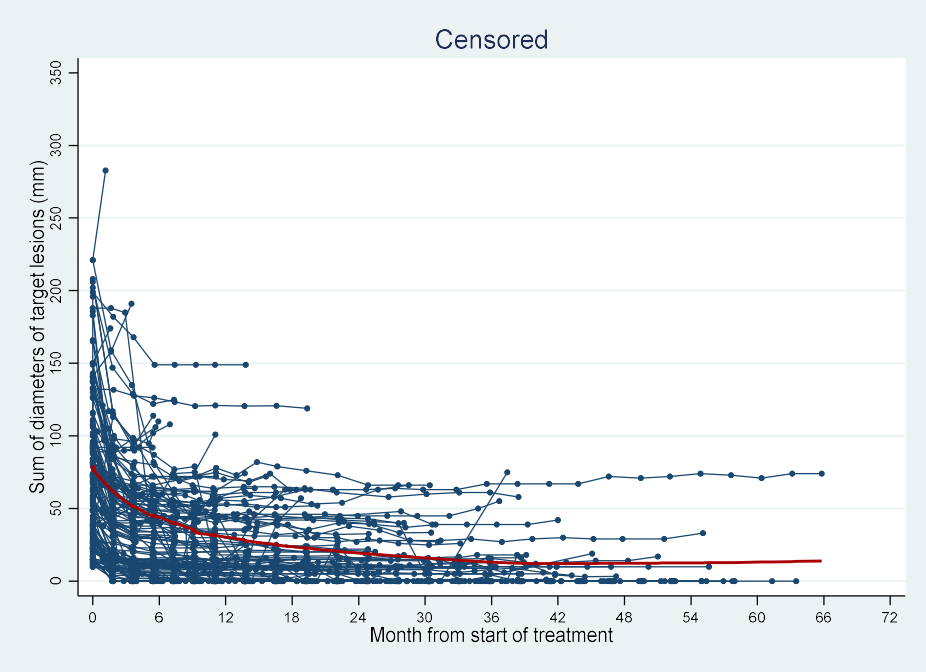
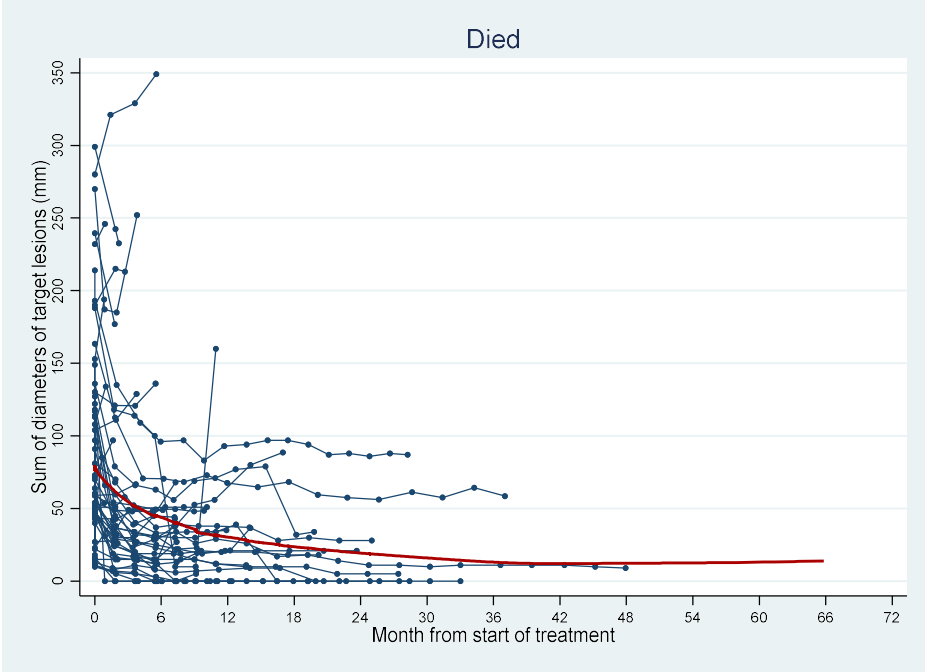
[1] Hong DS, Dubois SG, Kummar S et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncology 2020; 21(4): 531-540

Intermediate biomarker: Sum of diameters of target lesions (mm)

Patient trajectories





Lowess smoothing

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Joint model specification

- Bayesian joint model (fitted using MCMC in JAGS):
  - Repeated measures linear regression submodel for tumour burden biomarker
  - Weibull submodel for overall survival
- Submodels linked by an association parameter:
  - Absolute (current) value
  - Change from baseline (slope association)

MCMC: Markov chain Monte Carlo, JAGS: Just Another Gibbs Sampler

Joint model specification

- 3 joint models were fitted with different assumptions about the association parameter in relation to **tumour type**:
  - > **Common** (one association parameter for all tumour types)
  - > **Exchangeable** (tumour-specific association parameters, “borrows strength”)
  - > **Independent** (tumour-specific association parameters, hierarchical)

- Patient-specific predictions of overall survival were then extrapolated from the joint models
- Compared to predictions from a standard parametric Weibull model.

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Association parameters between tumour burden and overall survival for the 3 joint models

Model	Tumour type	Events/patients	Association hazard ratio	95% Credible interval
Common	All tumours	58/196	1.09	1.05 to 1.14
Exchangeable	Soft tissue sarcoma	13/65	1.10	1.00 to 1.22
	Lung	5/23	1.08	1.00 to 1.18
	Salivary gland	6/25	1.05	0.83 to 1.18
	Thyroid	9/30	1.01	1.03 to 1.20
	Other	25/53	1.08	1.03 to 1.14
Independent	Soft tissue sarcoma	13/65	1.12	0.94 to 1.27
	Lung	5/23	1.08	0.87 to 1.23
	Salivary gland	6/25	0.78	0.59 to 1.09
	Thyroid	9/30	1.15	1.03 to 1.27
	Other	25/53	1.08	1.02 to 1.14

- Association HR is the increase in the risk of mortality per 10mm increase in tumour burden

Extrapolated survival results from the 3 joint models and a Weibull proportional hazards (PH) model

Model	Restricted mean survival time (years), 95% CrI	Median (years), 95% CrI	Landmark survival at 10 years (%), 95% CrI	Model fit (DIC)
Weibull PH	8.04 (4.88 to 13.44)	4.91 (3.25 to 6.57)	27.7 (13.7 to 39.8)	-
Common	8.46 (5.11 to 13.84)	4.54 (3.46 to 5.96)	27.6 (16.3 to 38.8)	16265
Exchangeable	8.88 (5.59 to 14.58)	4.58 (3.57 to 5.98)	28.1 (17.3 to 38.3)	15974
Independent	12.08 (7.22 to 17.80)	4.89 (3.70 to 6.40)	32.7 (21.43 to 40.31)	16018

- N=196 patients, 58 events
- Current value association structure linking tumour biomarker to overall survival

PH: proportional hazards, CrI: credible interval, DIC: deviance information criteria

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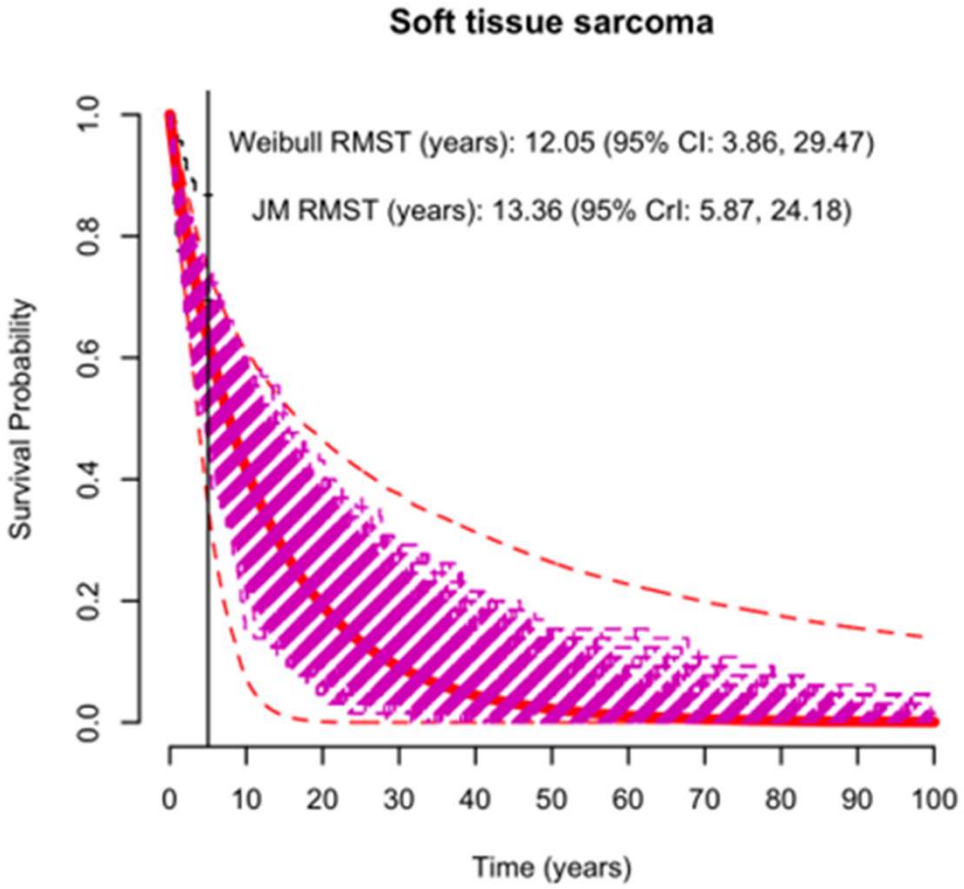
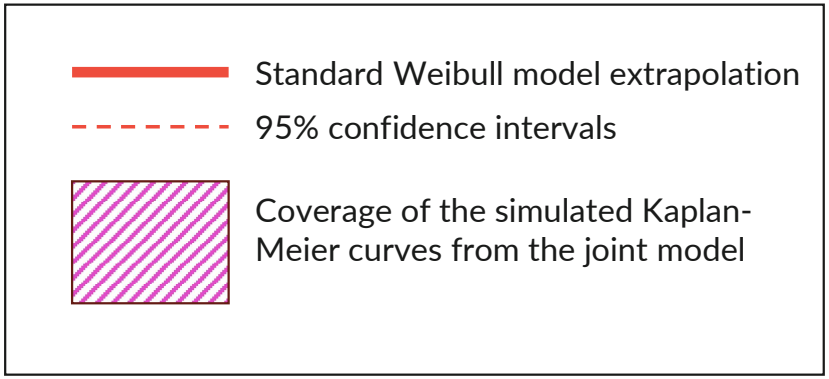
Tumour-specific survival predictions – Joint Model (exchangeable)





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Joint Modelling: potential benefits

- Estimate biomarker trajectories, **adjusting for informative drop-out**
- Estimate the **association between survival and the biomarker**, accounting for uncertainty in the biomarker trajectory
- **Provide patient-specific survival predictions** based on biomarker profiles up to the time of censoring
- **Hierarchical modelling** can be used for clustered data to provide subgroup-specific estimates of the association parameter and overall survival
- Can fit more than one biomarker/time-to-event outcome simultaneously in a **multivariate joint model**, with the correlation structure between them modelled appropriately

Joint Modelling: potential downfalls

- More complicated to fit than standard parametric models
- Exchangeable models can be sensitive to the choice of prior distribution, when there is a lack of information within each subgroup
- Hierarchical modelling requires adequate numbers of patients/events within each cluster/subgroup

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