Joint Modelling of Longitudinal and Survival Data Applied to Group Sequential Trials

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Joint modelling - Case study

Example: Taylor et. al. (2013) A clinical trial for the treatment of prostate cancer.

Process 1:

- Longitudinal data measured with error
- Prostate specific antigen (PSA) measurements from a blood test

Process 2:

- Overall survival

Potential benefits

By including the longitudinal data in the analysis, we hope to see:

- Fewer patients recruited to achieve power of 0.9 at $\theta = \delta$
- Increased information at interim analyses
- Early stopping for futility

Joint model

Longitudinal data model:

$$W_i(t) = X_i(t) + \epsilon_i(t)$$

- $X_i(t)$ true underlying trajectory e.g $X_i(t) = b_{0i} + b_{1i}t$
- $W_i(t)$ observed longitudinal measurements
- $\epsilon_i(t) \sim N(0, \sigma^2)$ measurement error

Time-to-event model:

$$\lambda_i(t) = \lambda_0(t)\exp(\gamma X_i(t) + \theta T_i + \boldsymbol{\eta}^T \mathbf{Z_i})$$

- $\lambda_0(t)$ baseline hazard rate
- T_i treatment indicator
- θ treatment effect
- $\mathbf{Z}_i$ patient covariates

Fixed sample trial - Analysis

Hypothesis test:

θ is the treatment effect. Test the (one-sided) hypothesis

$$H_0 : \theta = 0,$$
$$H_A : \theta > 0.$$

To perform the hypothesis test, choose:

- α significance level
- $1 - \beta$ desired power at δ
- δ minimum clinically significant effect size

Then determine:

- $\hat{\theta}$ - estimate of θ
- distribution of $\hat{\theta}$

Fixed sample trial - Theory

Aim:

Find $\hat{\theta}$, an estimate of θ.

The standard Cox model (without longitudinal data) states:

$$\lambda_i(t) = \lambda_0(t) \exp\{\theta T_i + \boldsymbol{\eta}^T \mathbf{Z}_i\} \tag{1}$$

and we can estimate θ by maximum partial likelihood.
For our joint model, we have

$$\lambda_i(t) = \lambda_0(t) \exp\{\gamma X_i(t) + \theta T_i + \boldsymbol{\eta}^T \mathbf{Z}_i\} \tag{2}$$

and maximum partial likelihood estimation requires integration over the $2n$ random effects in the model for $X_i(t)$.

Fixed sample trial - Theory

Aim:

Find $\hat{\theta}$, an estimate of θ and determine the distribution of $\hat{\theta}$.

We follow the approach of Tsiatis and Davidian (2001) to fit the joint model using the techniques:

- Estimating equations
- Conditional score

This gives an estimate $\hat{\theta}$ with known large sample distribution

$$\hat{\theta} \sim N(\theta, \mathcal{I}^{-1})$$

where $\mathcal{I}$ can be calculated from the data.

Fixed sample model comparisons

We are interested in comparing the Cox model and the joint model.

1. Simulate 100,000 datasets of n patients under the joint model. In this example, there is no $\boldsymbol{\eta}^T \mathbf{Z}_i$
2. Fit each dataset to the Cox model, equation (1) and estimate θ by maximum partial likelihood
3. Find the proportion of simulated clinical trials which reject the null hypothesis
4. Repeat steps 1-3, varying n until achieving power of 0.9
5. Call this value n_1

Fixed sample model comparisons

1. Simulate 100,000 datasets of n patients under the joint model. In this example, there is no $\boldsymbol{\eta}^T \mathbf{Z}_i$
2. Fit each dataset to the joint model, equation (2) and estimate θ by the conditional score
3. Find the proportion of simulated clinical trials which reject the null hypothesis
4. Repeat steps 1-3, varying n until achieving power of 0.9
5. Call this value n_2

Fixed sample efficiency results

Relative efficiency

$$\text{Relative efficiency} = \frac{n_1}{n_2}$$

Relative efficiency > 1: With analysis using the joint model, we require fewer patients in order to achieve power 0.9 than when using the simple Cox model.

Contributing factors

Reminder: $\lambda_i(t) = \lambda_0(t)\exp(\gamma X_i(t) + \theta T_i + \boldsymbol{\eta}^T \mathbf{Z_i})$.

- γ - controlling the contribution of the longitudinal data to the partial likelihood
- σ^2 - longitudinal measurement error
- Number of longitudinal observations

Fixed sample efficiency results

Fix the treatment effect $\theta = 0.6$.

			γ		
			0	0.02	0.04
σ^2	0	Cox model	115	189	246
		Joint model	118	117	118
		Relative efficiency	**0.973**	**1.621**	**2.083**
	25	Cox model	115	189	245
		Joint model	124	121	124
		Relative efficiency	**0.935**	**1.562**	**1.981**
	100	Cox model	116	187	244
		Joint model	130	131	160
		Relative efficiency	**0.894**	**1.434**	**1.524**

Extension to group sequential trials (GSTs)

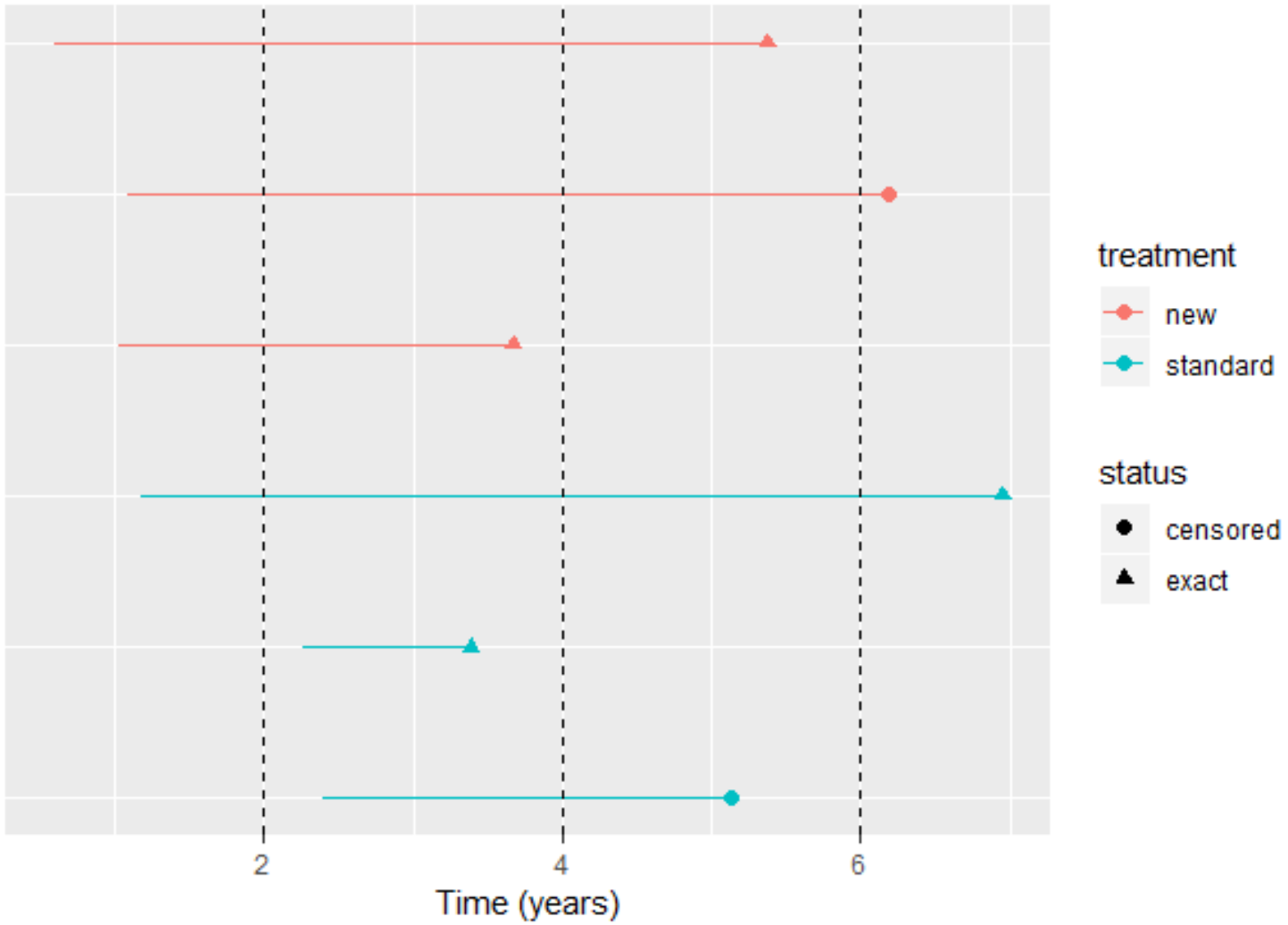


Figure: Entry and follow up times of patients in a GST measuring OS as the primary endpoint. Interim analyses occur at 2, 4 and 6 years.

Extension to group sequential trials (GSTs)

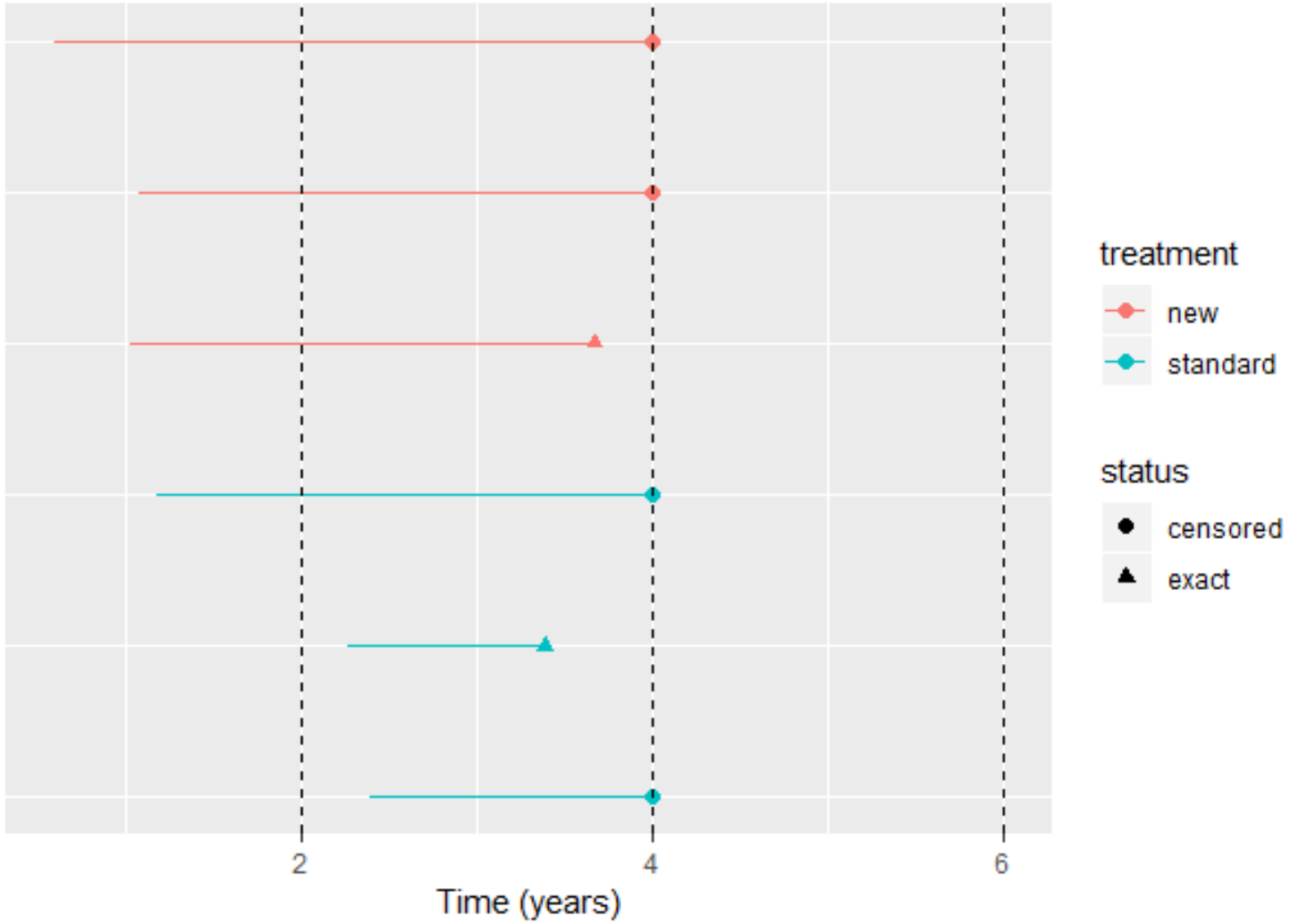


Figure: Data available in the GST at interim analysis at 4 years.

Extension to group sequential trials (GSTs)

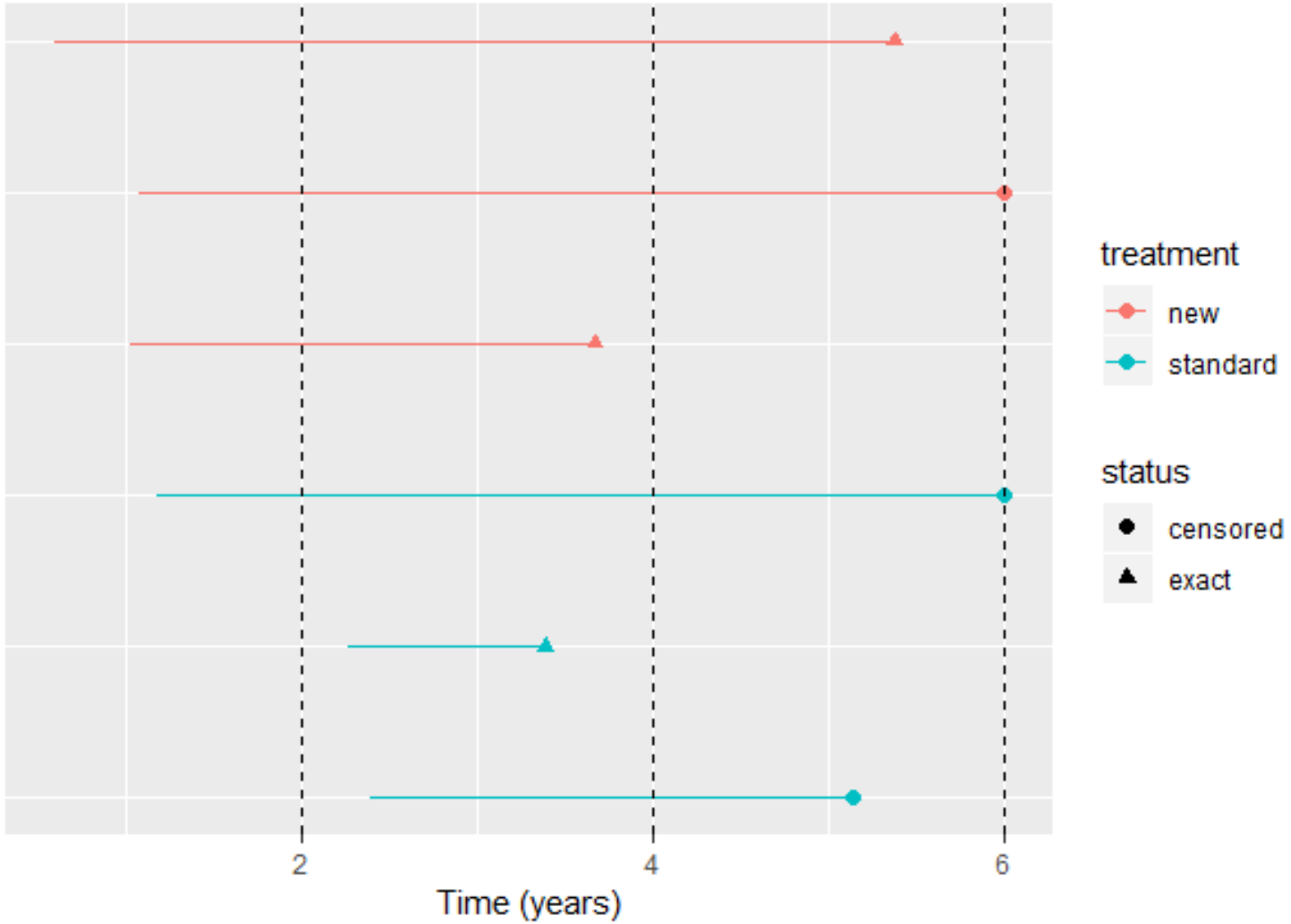


Figure: Data available in the GST at interim analysis at 6 years.

Extension to GSTs - Theory

The canonical joint distribution of a sequence of estimates:
Let $\hat{\theta}_1, \ldots, \hat{\theta}_K$ be a sequence of treatment effect estimates given by data available at interim analyses $1, \ldots, K$ respectively. Then the *canonical joint distribution* for this sequence is:

1. $(\hat{\theta}_1, \hat{\theta}_2, \ldots, \hat{\theta}_K)$ is multivariate normal,
2. $\mathbb{E}(\hat{\theta}_k) = \theta, k = 1, \ldots, K$,
3. $Cov(\hat{\theta}_{k_1}, \hat{\theta}_{k_2}) = Var(\hat{\theta}_{k_2})$, for $k_1 < k_2$

Jennison and Turnbull (2000) show that show the canonical joint distribution holds for a variety of data types.

New result:

We can extend conditional score to GSTs to show that the sequence $\hat{\theta}_1, \ldots, \hat{\theta}_K$ generated by fitting the joint model follows the canonical joint distribution.

Group sequential efficiency results

Relative efficiency for a group sequential trial with:

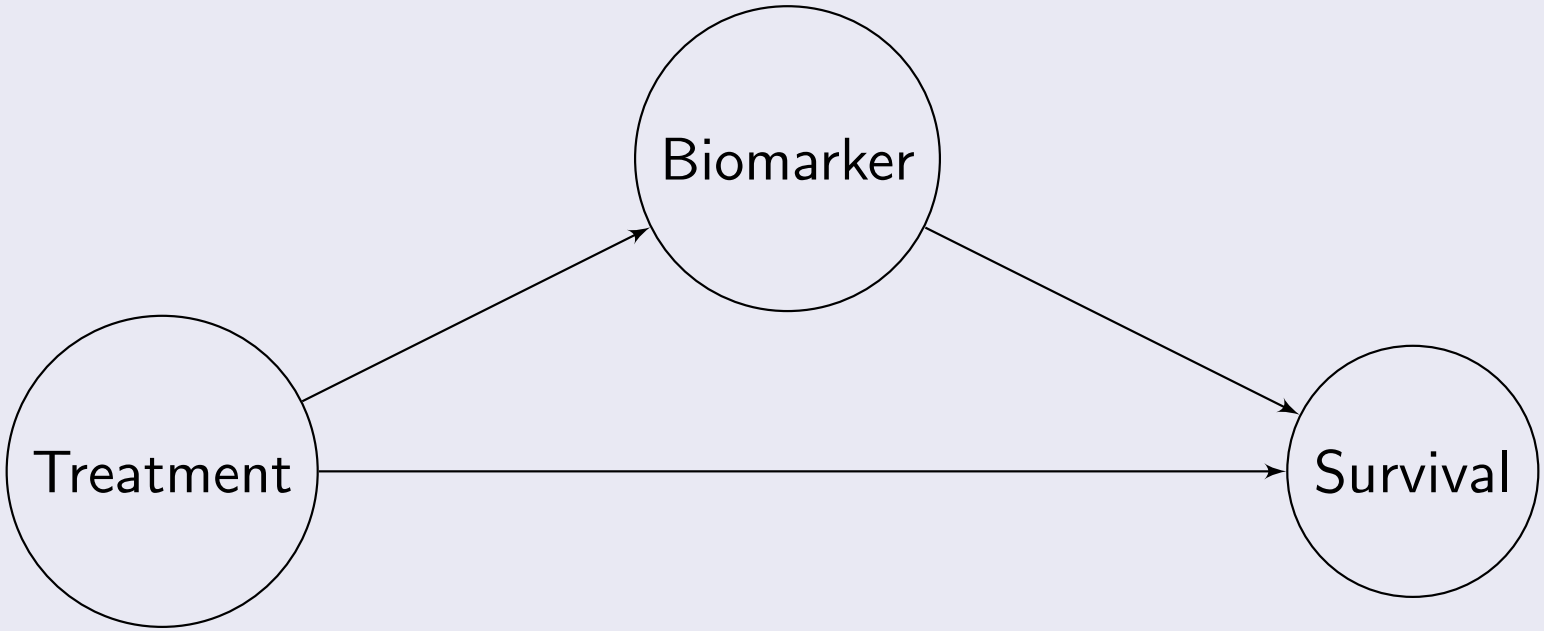
- 2 years recruitment, 3 years follow up
- 5 interim analyses equally spaced in time
- Error spending functions for both efficacy and futility boundaries

			γ	
		0	0.02	0.04
σ^2	0	Cox model	186	218	309
		Joint model	195	143	138
		Relative efficiency	**0.957**	**1.522**	**2.248**
	25	Cox model	186	218	307
		Joint model	207	153	151
		Relative efficiency	**0.900**	**1.429**	**2.032**
	100	Cox model	189	215	308
		Joint model	223	169	179
		Relative efficiency	**0.849**	**1.275**	**1.719**

Future research

Indirect treatment effect:

Account for treatment acting through two pathways.



Challenge: How to summarise overall treatment effect as a combination of the "direct" and "indirect" treatment effects.

Future research

Non-binding futility boundary

Suppose the regulator is not convinced that your joint model is correct so you are required to demonstrate a treatment effect by a (sequential) logrank test. You would like to do this and use the longitudinal data to help guide early stopping for futility.

Adapt the group sequential trial to have an efficacy boundary based on a log-rank statistic and a non-binding futility boundary that uses the jont model.

Challenge: Find a joint distribution for the log-rank statistics and joint model treatment effect estimates accross interim analyses.


Christopher Jennison and Bruce W Turnbull.
Group sequential methods with applications to clinical trials.
Chapman and Hall/CRC, 2000.


Jeremy MG Taylor, Yongseok Park, Donna P Ankerst, Cecile Proust-Lima, Scott Williams, Larry Kestin, Kyoungwha Bae, Tom Pickles, and Howard Sandler.
Real-time individual predictions of prostate cancer recurrence using joint models.
Biometrics, 69(1):206–213, 2013.


Anastasios A Tsiatis and Marie Davidian.
A semiparametric estimator for the proportional hazards model with longitudinal covariates measured with error.
Biometrika, 88(2):447–458, 2001.

Thank you for listening.

Any questions?