Flexible and Robust Bayesian Information Borrowing for Clinical Trials with Longitudinal Outcomes

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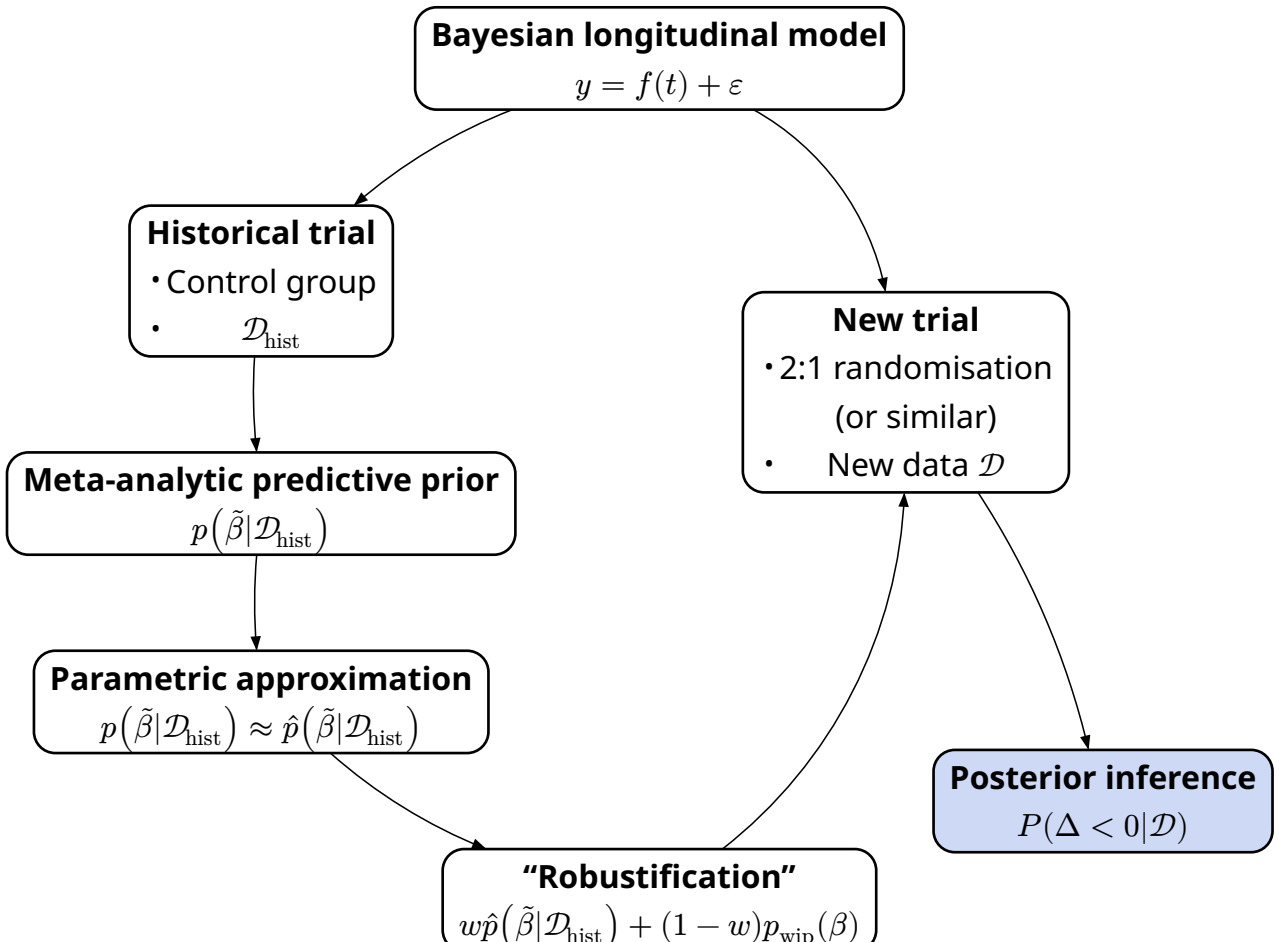
Background & Motivation

- Design and analysis of RCTs in rare disease and/or paediatric indications
  → Small sample sizes, underpowered trials
- Bayesian information borrowing methods as a remedy to incorporate external information
  - Increase efficiency / Reduce sample size in new trial (+)
  - Risk of bias / type I error inflation (-)
  - FDA draft guidance on Bayesian Methodology in Clinical Trials (Food and Drug Administration, 2026)
- Further options to increase efficiency of clinical trials (Day et al., 2018)
  - Information-rich endpoints (continuous instead of dichotomous)
  - Longitudinal data
  - ...
- Only few information borrowing methods for longitudinal data settings

Method Overview

- Bayesian hierarchical modelling
- Natural cubic splines for continuous-time longitudinal modelling (Donohue et al., 2023)
- Robust meta-analytic-predictive priors for control group information borrowing (Schmidli et al., 2014)



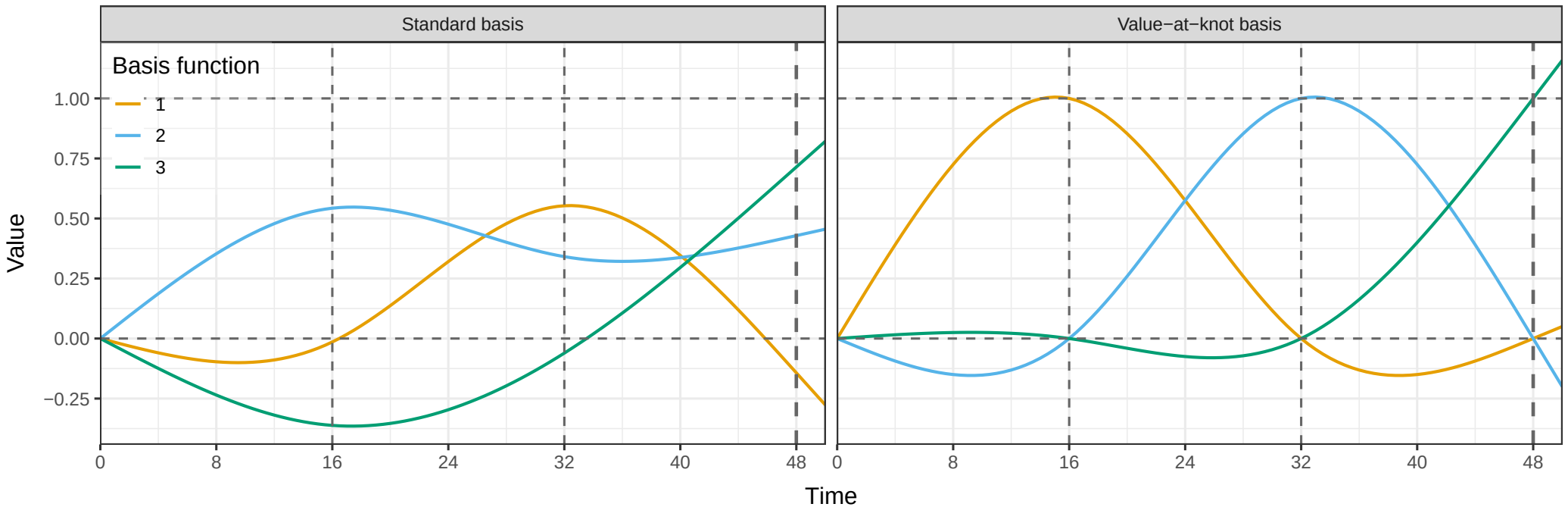
Longitudinal Model

$$\overbrace{y_{ij}}^{\text{Continuous outcome}} = \beta_0 + \sum_{k=1}^{l} \beta_k b_k(t_{ij}) + a_i \sum_{k=1}^{l} \gamma_k b_k(t_{ij}) + u_{i0} + \sum_{k=1}^{l} u_{ik} b_k(t_{ij}) + \varepsilon_{ij}$$

$$= \underbrace{\beta_0}_{\text{Common baseline mean}} + \underbrace{\boldsymbol{x}'_{ij}\boldsymbol{\beta}}_{\text{Control group mean trajectory}} + \underbrace{\tilde{\boldsymbol{x}}'_{ij}\boldsymbol{\gamma}}_{\text{Treatment group offsets}} + \underbrace{\boldsymbol{z}'_{ij}\boldsymbol{u}_i}_{\text{Subject-specific effects}} + \underbrace{\varepsilon_{ij}}_{\text{Residual error}}$$

- $i = 1, ..., m$ (subjects), $j = 1, ..., n_i$ (observations within subject at visit times t_{ij})
- Constrained longitudinal data analysis (cLDA) parametrisation (Liang & Zeger, 2000)
  - Common intercept β_0, justified by randomisation
- $b_k(t_{ij})$: Natural cubic spline basis functions
  - Number and location of knots
- Treatment effect: $\Delta(t^*) = \tilde{\boldsymbol{x}}'_* \boldsymbol{\gamma}$
  - *Mean difference in change from baseline*

Natural Cubic Splines



- Transformed basis: $\tilde{\boldsymbol{B}}(\boldsymbol{x}) = \boldsymbol{B}(\boldsymbol{x})\boldsymbol{B}(\boldsymbol{k})^{-1}$ ($\boldsymbol{k}$ vector of knot locations)
- Change from baseline interpretation at knot locations
  → Similar to MMRM (mixed model for repeated measurements)

Prior Distributions

$$y_{ij} = \beta_0 + \boldsymbol{x}'_{ij}\boldsymbol{\beta} + \tilde{\boldsymbol{x}}'_{ij}\boldsymbol{\gamma} + \boldsymbol{z}'_{ij}\boldsymbol{u}_i + \varepsilon_{ij}$$

- Weakly informative prior distributions (Gelman et al., 2021, chapter 2) / Unit-information priors (Kass & Wasserman, 1995)
- Ingredients for pre-specification
  - $\hat{\sigma}$: Assumed standard deviation of the outcome at the final visit
  - $\hat{y}_0$: Assumed population mean at baseline
  - $\hat{y}_{t^*}$: Assumed population mean at final visit (control group)
- **No borrowing yet!**

- $\beta_0 \sim \mathcal{N}\left(\hat{y}_0, \hat{\sigma}/\sqrt{2}\right)$
- $\beta_k \sim \mathcal{N}(\delta_k, \hat{\sigma}), \quad k = 1, ..., l$
  - $\delta_k = \frac{k}{l}(\hat{y}_{t^*} - \hat{y}_0)$
- $\gamma_k \sim \mathcal{N}(0, s_k), \quad k = 1, ..., l$
  - $s_k = \hat{\sigma}/\sqrt{2 - \frac{k}{l}}$
- $\boldsymbol{u}_i \sim \mathcal{N}_{l+1}(\boldsymbol{0}, \boldsymbol{Q}_u), \quad i = 1, ..., m$
- $\boldsymbol{Q}_u = \boldsymbol{DPD}$
  - $\boldsymbol{D} = \text{diag}(\tau_0, \tau_1, ..., \tau_l)$
  - $\boldsymbol{P}$: Correlation matrix
- $\tau_k \sim \mathcal{N}_+(0, \hat{\sigma}), \quad k = 0, 1, ..., l$
- $\boldsymbol{P} \sim \text{LKJ}(1)$ (Lewandowski et al., 2009)
- $\sigma \sim \mathcal{N}_+(0, \hat{\sigma})$

Meta-analytic-predictive (MAP) Prior

$$y_{ijs} = \beta_0 + \boldsymbol{x}'_{ijs}\boldsymbol{\beta} + \boldsymbol{z}'_{ijs}\boldsymbol{u}_i + \boldsymbol{z}'_{ijs}\boldsymbol{v}_s + \varepsilon_{ij}$$

- $\boldsymbol{v}_s$: Second level of group effects for between-trial heterogeneity

$$\boldsymbol{v}_s \sim \mathcal{N}_{l+1}(\boldsymbol{0}, \boldsymbol{Q}_v), \quad s = 1, ..., S'$$
$$\boldsymbol{Q}_v = \mathrm{diag}(\omega_0, \omega_1, ..., \omega_l)$$
$$\omega_k \sim p_{\omega_k}, \quad k = 0, 1, ..., l$$

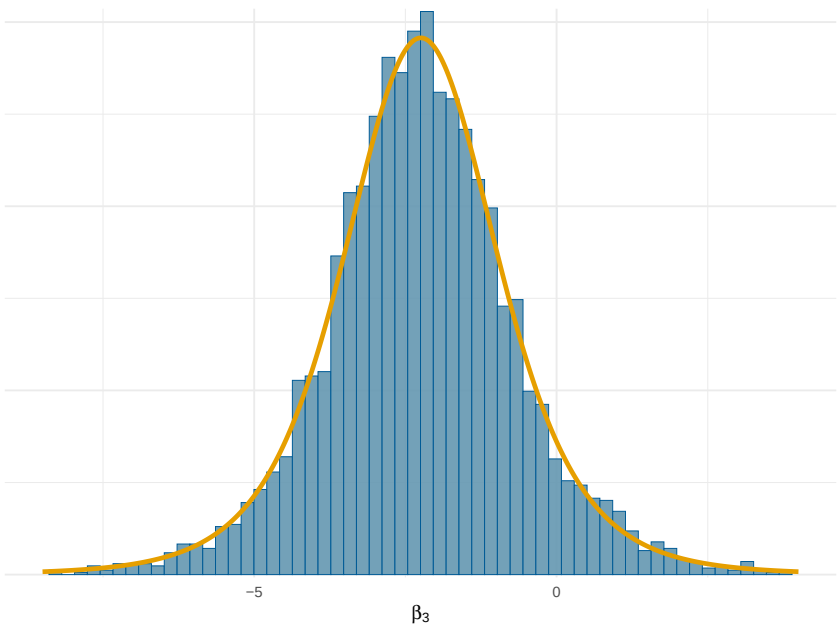
- Prior p_{ω_k} critical for few or even one study (Röver & Friede, 2026)
- MAP prior: Posterior "predictive" distribution of the population-level effects for a new study $\tilde{\beta}$ (Neuenschwander et al., 2010)

$$p\left(\tilde{\beta}_k \mid \mathcal{D}_{\text{hist}}\right) = \iint p(\beta_k, v_{\cdot k}, \omega_k \mid \mathcal{D}_{\text{hist}})\, dv_{\cdot k}\, d\omega_k$$

MAP Prior Approximation & “Robustification”

Approximation

- MAP prior typically available as set of MCMC draws
- Parametric representation/approximation required (here student-t distribution)



Robustification

- MAP prior already heavy-tailed and capable of mitigating moderate prior-data conflicts
- Additional protection by adding weakly informative component (Schmidli et al., 2014)

$$p(\beta_k) = w_k p\left(\tilde{\beta}_k \mid \mathcal{D}\right) + (1 - w_k) p_{\text{wip}}(\beta_k)$$

- $p_{\text{wip}}(\beta_k)$: Unit-information normal prior (Kass & Wasserman, 1995) or modified version thereof (Weru et al., 2026)

Simulation Study Setup

Methods

- Bayesian spline model (no borrowing)
- Bayesian spline rMAP model (1)
  - $(w_0, w_1, w_2, w_3)' = (0.5, 0.25, 0.25, 0.25)'$
- Bayesian spline rMAP model (2)
  - $(w_0, w_1, w_2, w_3)' = (0.5, 0.4, 0.25, 0.1)'$

Comparators

- MMRM current trial
- MMRM pooled data

Estimands and targets

- $\Delta(t^*)$ at $t^* = 48$ weeks
- $H_0 : \Delta(t^*) \geq 0 \quad \text{vs.} \quad H_1 : \Delta(t^*) < 0 \quad (\alpha = 2.5\%)$

Performance measures

- Type I error and power
- (Bias, MSE)
- (CI coverage and width)

Computational details

- 1,000 repetitions for each scenario
- Bayesian models written and fit in/via Stan (Carpenter et al., 2017) and `cmdstanr` R package (Gabry et al., 2025)
- MCMC: 4 chains, 1,000 draws each
- MMRMs fit via `mmrm` R package (Sabanes Bove et al., 2026)

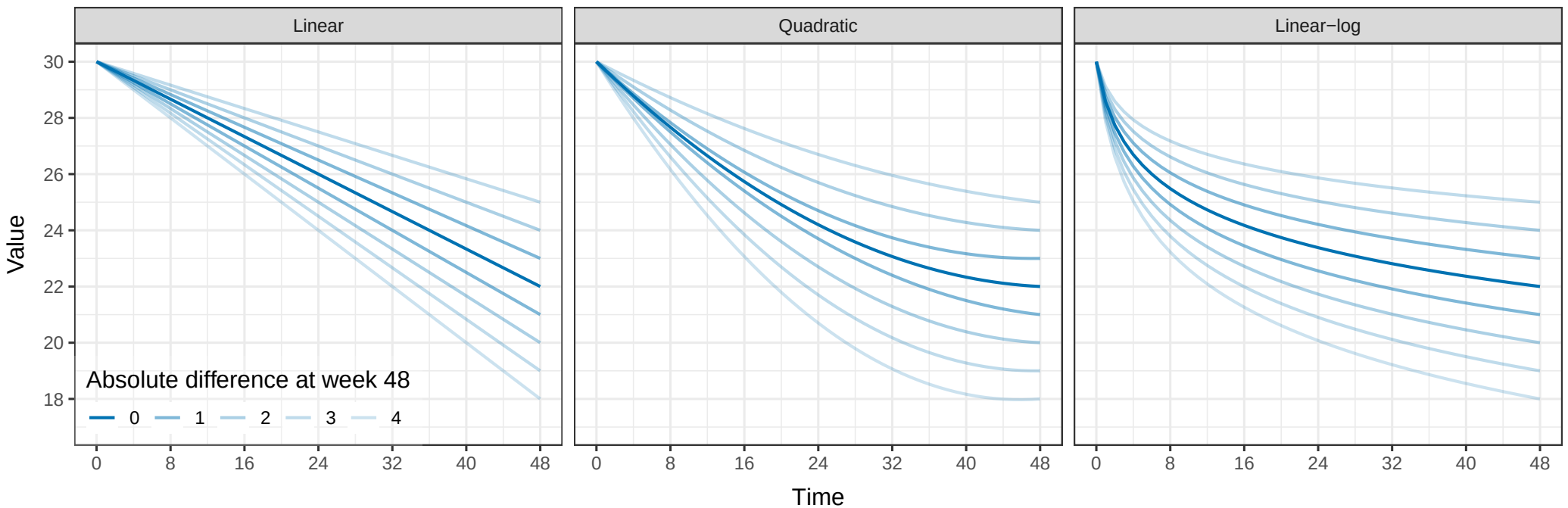
Data-generating Mechanisms

- 7 visits (including baseline): $t_k = 8k, k \in \{0, 1, ..., 6\}$
- $(n_{\text{trt}}, n_{\text{ctrl}})' = (60, 30)$
- $\boldsymbol{y}_i \sim \mathcal{N}_7(\boldsymbol{\mu}_i, \Sigma)$
- Σ: First-order ante-dependence (Gabriel, 1962)
  - $\sigma_k = 6.3 + 0.45k, k \in \{0, 1, ..., 6\}$
  - $\rho_j = 0.875 + 0.015j, j \in \{0, 1, ..., 5\}$
- 10% missing completely at random (MCAR)

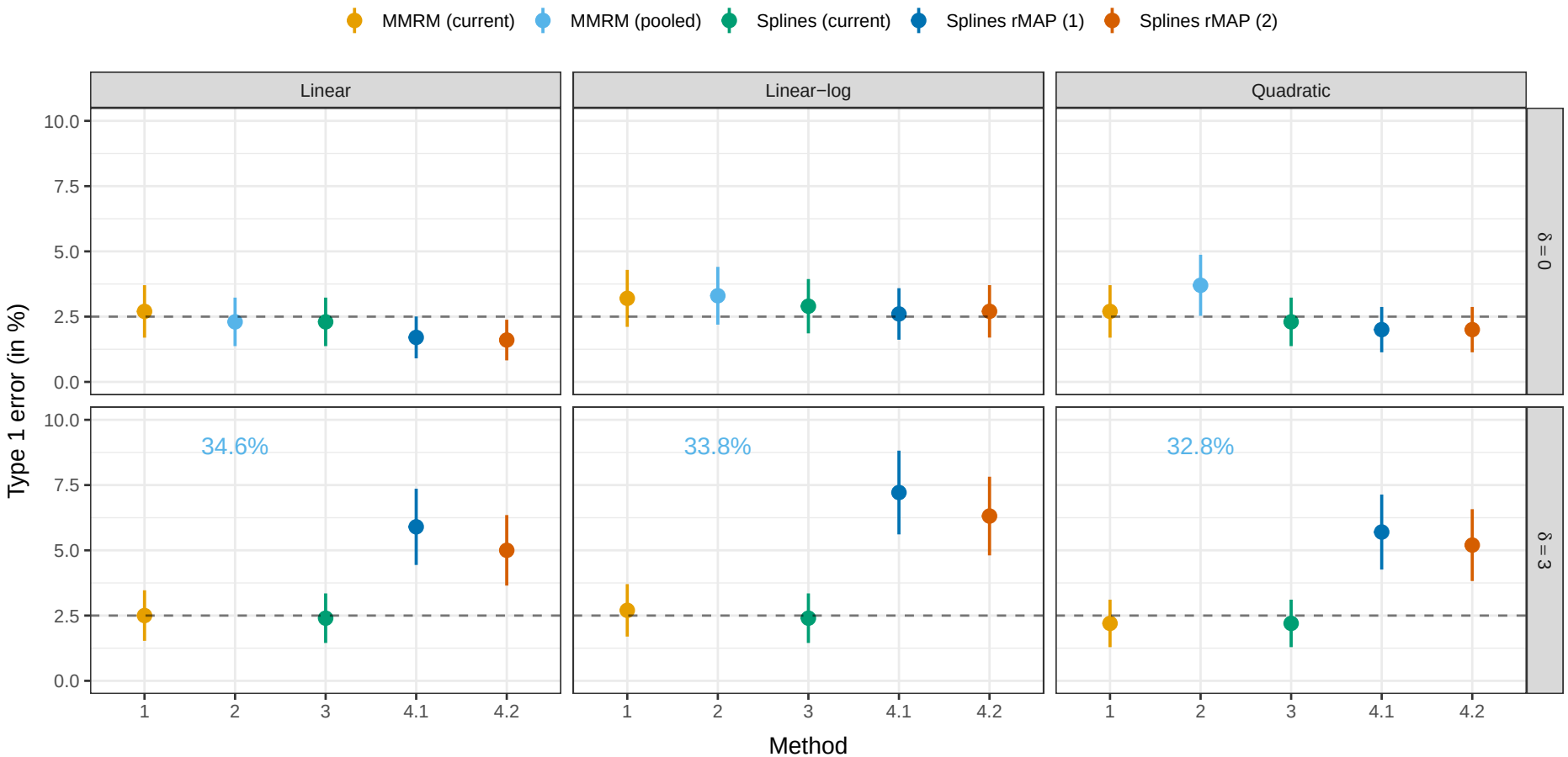
Parameter	Description	Values	#Values
$\mu(t)$	Longitudinal mean function	linear, linear-log, quadratic	3
Δ	Treatment effect at final visit	$0, -4$	2
n_{hist}	Historical control group sample size	$30, 60, 120$	3
δ	Mean difference at final visits	$0, \mp 1, \mp 2, \mp 3$	7
			Number of scenarios: 126

- Two-sample t-test using (complete) final visit data would yield power of 50%

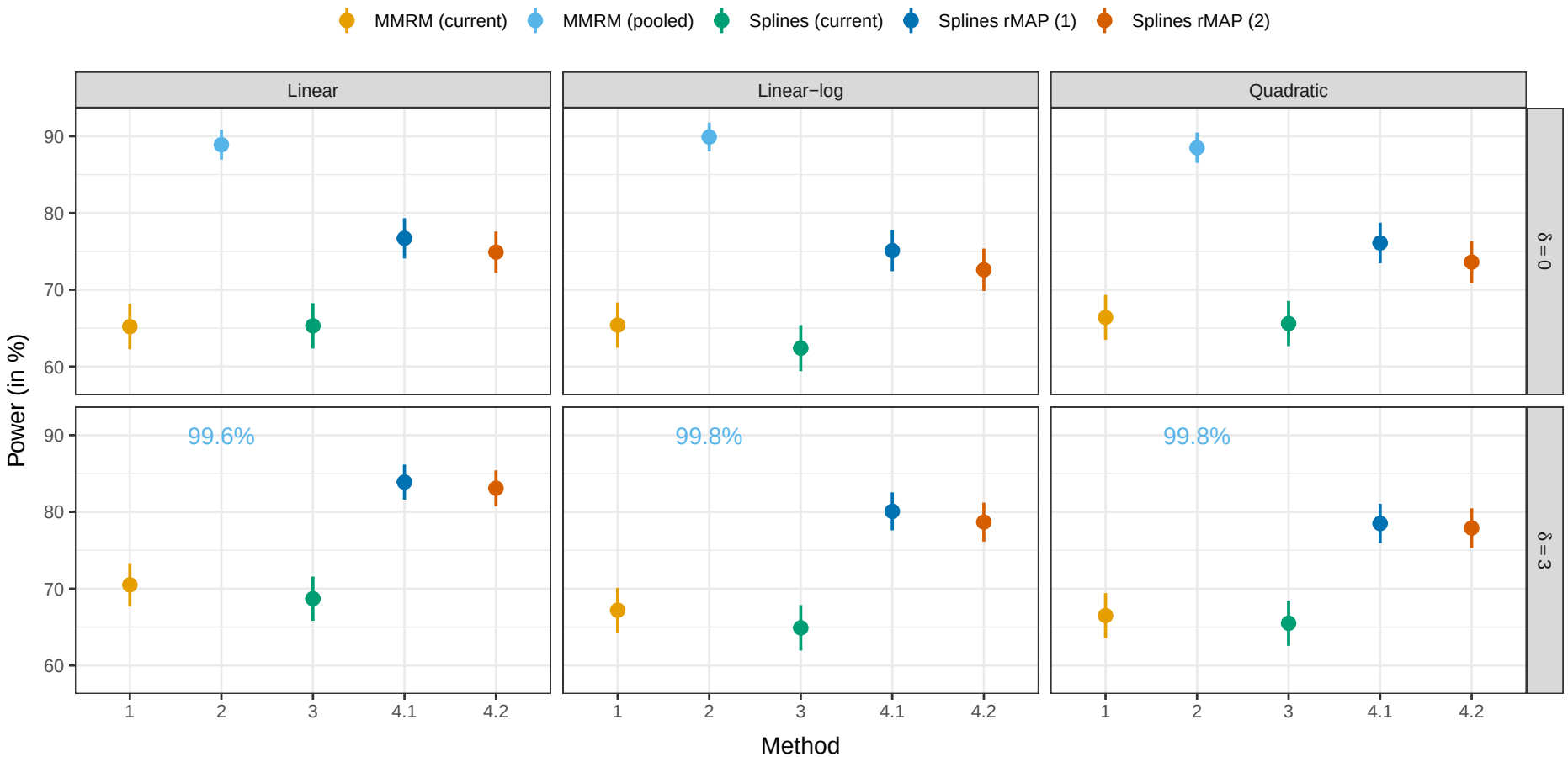
Data-generating Mechanisms – Mean Functions



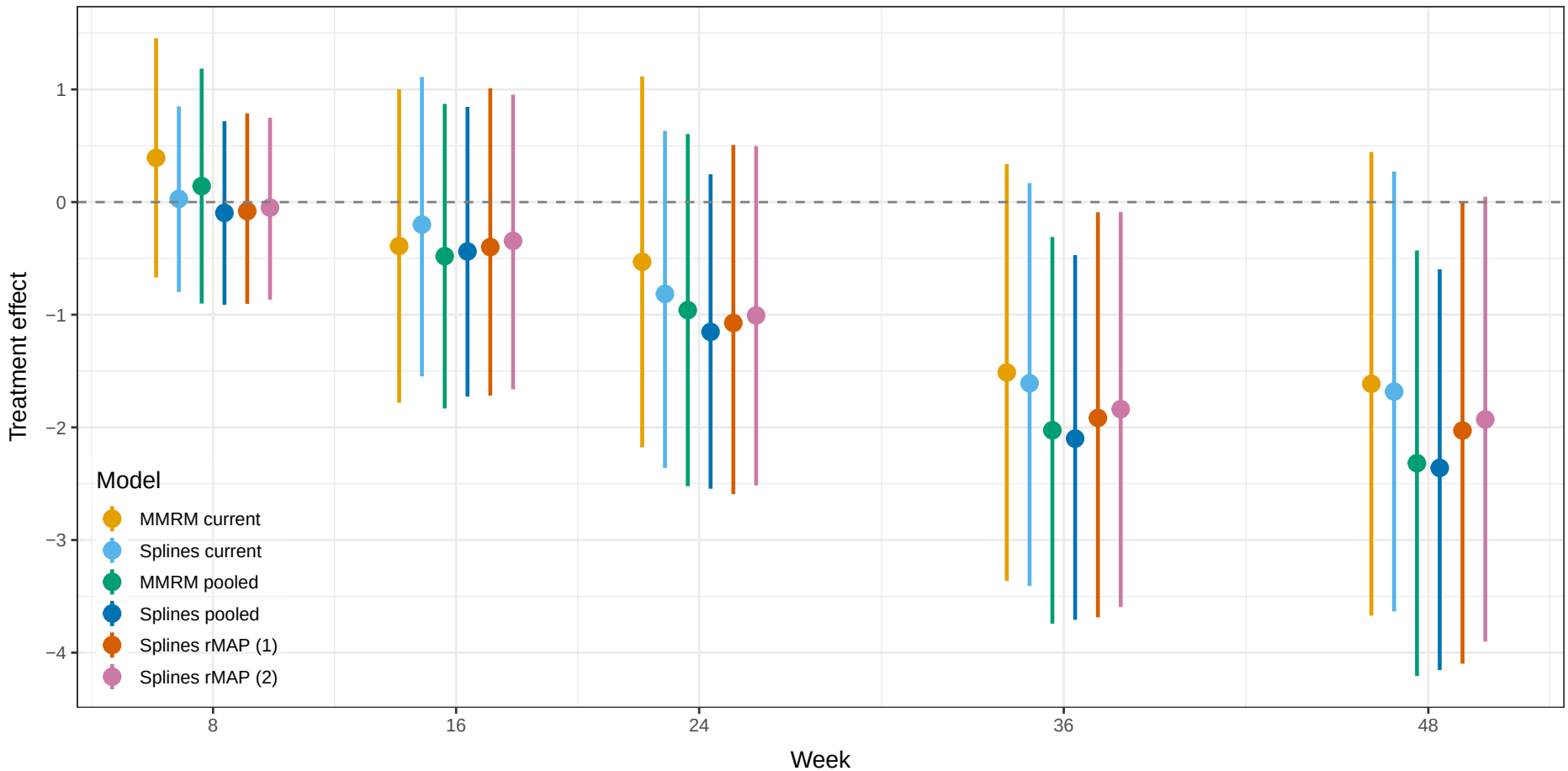
Simulation Results – Type I Error



Simulation Results – Power



Data Example – Systemic Sclerosis



Summary

- Combination of different approaches to increase efficiency of (small-sample) clinical trials
  - Longitudinal modelling of continuous endpoints
  - Bayesian information borrowing
- Limited number of proposed methods so far, each with limitations
  - Parametric modelling assumption (mean trajectories)
  - Discrete-time modelling can prohibit information borrowing
- Novel method proposal that is…
  - *Flexible* w.r.t. accurately modelling mean trajectories
  - *Efficient* by leveraging historical information
  - *Robust* in cases of prior-data conflict
  - *Interpretable* – Coefficients with change from baseline interpretation (as in MMRM)
- Open tasks/questions
  - Prior effective sample size (Neuenschwander et al., 2020)

Thank you for your attention

Speaker's Details

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