Challenges in RCTs solved with joint models?

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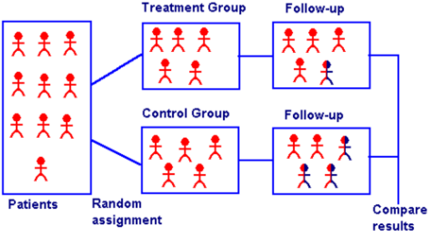
Overview

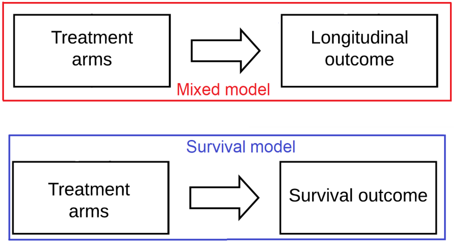
Randomized controlled trial

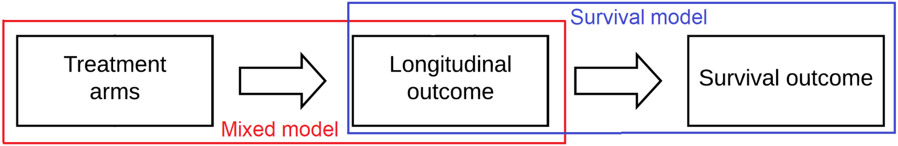


- A type of **clinical trial**
- Compares two (or more) groups:
  - Treatment vs. placebo
  - Or new treatment vs. existing treatment
  - Patients are randomly assigned to the groups
  - Goal: to assess the **treatment effect**

Joint models

- Joint models combine longitudinal and survival data
- Methods for a separate analysis are well established




Survival model
Treatment arms
Longitudinal outcome
Survival outcome
Mixed model


Mixed
Survival
better together ?

Joint models

- **Mixed effects model**

$$\begin{aligned} y_i(t) &= m_i(t) + \epsilon_i(t) \\ &= x_i^\top(t)\beta + z_i^\top(t)b_i + \epsilon_i(t) \end{aligned}$$

- where $m_i(t)$ is the *true* and *unobserved* longitudinal outcome, with history $\mathcal{M}_i(t) = \{m_i(s), 0 \leq s < s\}$

Joint models

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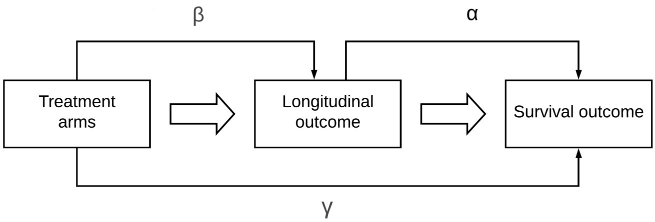
- **Survival model (Cox model)**

$$h_i(t|\mathcal{M}_i(t), w_i) = h_0(t)\exp\{\gamma^\top w_i + \alpha m_i(t)\}$$

- where α quantifies the *association* between the longitudinal outcome and the risk of an event

Overall treatment effect in a joint model

- Interest in the process of how a treatment affects a survival outcome (e.g., Alzheimer studies)



- The treatment effect is a combination of:
  - The (indirect) treatment effect in the longitudinal process
  - The (direct) treatment effect in the survival process

Overview

Overall treatment effect in a joint model

- **Mixed effects model**

$$\begin{aligned} y_i(t) &= m_i(t) + \epsilon_i(t) \\ &= \beta_0 + \beta_1 t + \boldsymbol{\beta_2}(t \times trt_i) + b_{i0} + b_{i1} t + \epsilon_i(t) \end{aligned}$$

- **Survival model**

$$h_i(t) = h_0(t) \exp\{\boldsymbol{\gamma} trt_i + \boldsymbol{\alpha} m_i(t)\}$$

- What is the **overall treatment effect**?

Overall treatment effect in a joint model

- **Mixed effects model**

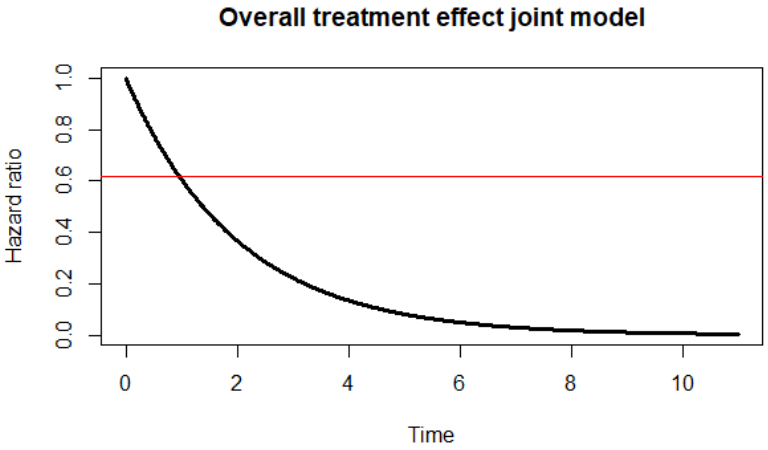
$$
\begin{aligned}
y_i(t) &= m_i(t) + \epsilon_i(t) \\
&= \beta_0 + \beta_1 t + \boldsymbol{\beta}_2 (t \times trt_i) + b_{i0} + b_{i1} t + \epsilon_i(t)
\end{aligned}
$$

- **Survival model**

$$
h_i(t) = h_0(t) \exp\{\boldsymbol{\gamma}\, trt_i + \boldsymbol{\alpha}\, m_i(t)\}
$$

- What is the **overall treatment effect**?
- First guess: $\boxed{\gamma + \alpha\beta_2 t}$

Overall treatment effect in a joint model



Overall treatment effect in a joint model

- Treatment effect is the hazard ratio between patient i (treatment) and patient i' (control)

$$\frac{h_i(t)}{h_{i'}(t)} = \frac{\exp[\gamma + \alpha\{\cancel{\beta_0} + \cancel{\beta_1 t} + \beta_2(t \times trt_i) + b_{i0} + b_{i1}t\}]}{\exp[\alpha\{\cancel{\beta_0} + \cancel{\beta_1 t} + b_{i'0} + b_{i'1}t\}]}$$

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$$= \exp\{\gamma + \alpha\beta_2 t + \alpha(b_{i0} + b_{i1}t - b_{i'0} + b_{i'1}t)\}$$

- Patient i and i' are two different patients, i.e., $b_i \neq b_{i'}$

Overall treatment effect in a joint model

- exp() is a non-linear link function

$$E[g(X)] \neq g(E[X])$$
$$E_b[g(\gamma + \alpha\beta_2 t + \alpha(Zb_i - Zb_{i'})] \neq g(E_b[\gamma + \alpha\beta_2 t + \alpha(Zb_i - Zb_{i'})])$$

- Average treatment effect $\neq$ the treatment effect for average subject
- The overall treatment effect $\boxed{\gamma + \alpha\beta_2 t}$ $\rightarrow$ **Subject-Specific (SS)** interpretation

Marginal and Subject-Specific effects

- Marginal and SS effects differ in **value** and **interpretation**
- **SS effects**
    - Conditional on the random effects
    - Individual-based inference (growth studies, personalized medicine)

  Marginal effects
    - Population averaged effects
    - Population-based inference (testing new drugs for efficacy)

Marginal versus Subject-Specific effects

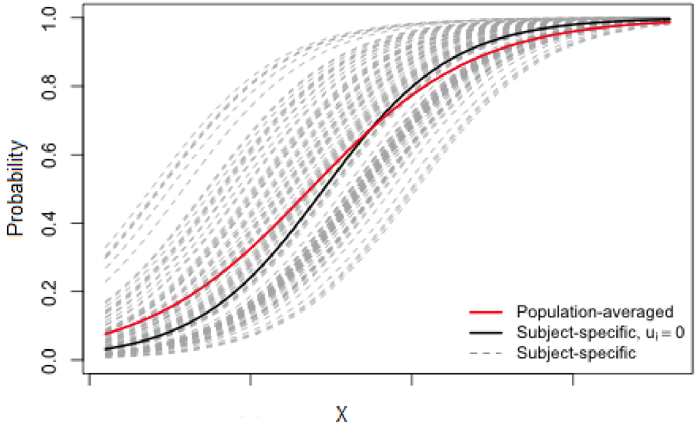
- **SS** overall treatment effect → effect of receiving the treatment instead of placebo for a specific patient, i.e., it is conditional on her random effects
- **Marginal** overall treatment effect → average treatment effect in population → currently not available

Marginal versus Subject-Specific effects

- Similar situation: Clustered longitudinal data with a binary outcome
  - SS approaches: Generalized Linear Mixed Models (GLMMs)
    - Mixed models are a special case of GLMMs
  - Marginal approaches: GEE, Marginalized Multilevel Model
  - [Hedeker, 2017] proposed a method for the marginalization of regression parameters of GLMM

Hedeker et al. (2017). A note on marginalization of regression parameters from mixed models of binary outcomes. Biometrics

Marginal versus Subject-Specific effects



The average probability $\neq$ probability for the average patient

Overview

Proposed method

- Goal: marginal overall treatment effect $\boxed{\gamma^M + \alpha^M \beta_2^M t}$
- Remember

$$h_i(t) = h_0(t) \exp\{\gamma^\top w_i + \alpha \underbrace{(x_i^\top(t)\beta + z_i^\top(t) b_i)}_{m_i(t)}\}$$

Proposed method

- Goal: marginal overall treatment effect $\boxed{\gamma^M + \alpha^M \beta_2^M t}$
- Remember

$$h_i(t) = h_0(t) \exp\{\gamma^\top w_i + \alpha \underbrace{(x_i^\top(t)\beta + z_i^\top(t) b_i)}_{m_i(t)}\}$$

- Consider the marginal log hazard ratio versus the baseline hazard

$$\log\left\{\frac{h_i(t)}{h_0(t)}\right\}^M = w_i^\top \gamma^M + \alpha^M \{x_i^\top(t)\beta^M\}$$

Proposed method

- Can be approximated numerically, e.g. by Monte Carlo integration

$$\log \left\{ \frac{h_i\hat{(}t)}{h_0(t)} \right\}^M \approx \log \int_b \exp[w_i^\top \gamma^{SS} + \alpha^{SS}\{x_i^\top(t)\beta^{SS} + z_i^\top(t)b_i\}]f(b)db$$

Proposed method

- Marginal log hazard ratio versus the baseline hazard

$$\log\left\{\frac{h_i(t)}{h_0(t)}\right\}^M = w_i^\top \gamma^M + \alpha^M \{x_i^\top(t)\beta^M\}$$

Proposed method

- Marginal log hazard ratio versus the baseline hazard

$$\log\left\{\frac{h_i(t)}{h_0(t)}\right\}^M = w_i^\top \gamma^M + \alpha^M\{x_i^\top(t)\beta^M\}$$

- Can be rewritten as

$$\log HR_i^M = w_i\gamma^M + x_i\alpha^M\beta^M = \tilde{X}_i\theta^M$$

Proposed method

- Marginal log hazard ratio versus the baseline hazard

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- Can be rewritten as

$$\log HR_i^M = w_i\gamma^M + x_i\alpha^M\beta^M = \tilde{X}_i\theta^M$$

- Where:

$$\tilde{X}_i = \begin{bmatrix} w_i & x_i \end{bmatrix} \qquad \theta^M = \begin{bmatrix} \gamma^M \\ \alpha^M\beta^M \end{bmatrix}$$

Proposed method

- $$\log HR_i^M = w_i\gamma^M + x_i\alpha^M\beta^M = \tilde{X}_i\theta^M$$

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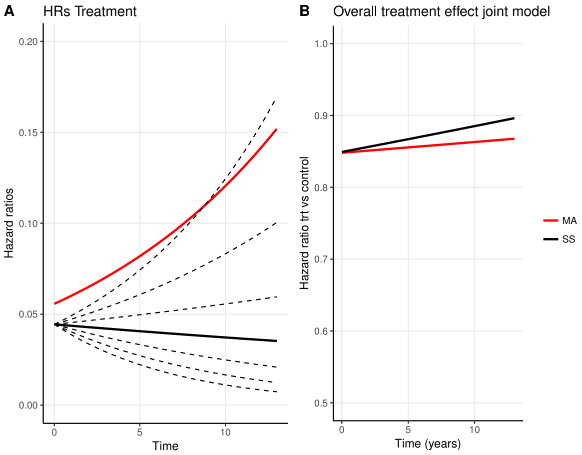
- $$\log HR_i^M = w_i\gamma^M + x_i\alpha^M\beta^M = \tilde{X}_i\theta^M$$
- Multiplying both sides by $(\tilde{X}^\top\tilde{X})^{-1}\tilde{X}^\top$:
$$\theta^M = \left(\sum_{i=1}^{N+n} \tilde{X}_i^\top \tilde{X}_i\right)^{-1} \left(\sum_{i=1}^{N+n} \tilde{X}_i^\top \log HR_i^M\right)$$
- Gives us: $\boxed{\gamma^M + \alpha^M\beta_2^M t}$

Results proposed method

- As an example we use the available Prothro dataset
- 488 patients with liver cirrhosis
- Longitudinal outcome: prothrombin
- Survival outcome: patient survival
- Goal:
    - Compare the marginal and SS overall treatment effect on patient survival
    - Compare the marginal and SS hazard ratios ($\log HR_i^M$ vs. $\log HR_i^{SS}$)

Results proposed method

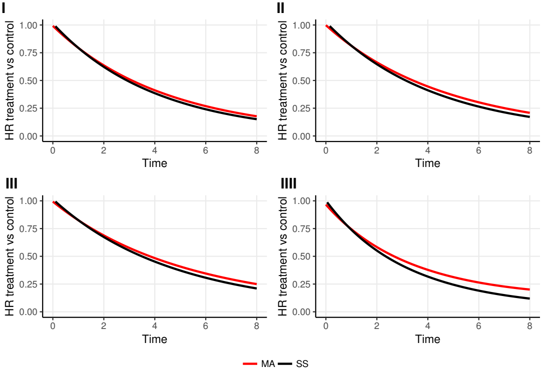


A) Hazard ratios versus the baseline hazard
B) Overall treatment effect

Simulation study

- We investigated the effect of two parameters:
  - The association parameter α
  - The variance of the random slope $\Sigma_{b_1^2}$

Simulation study



1) α = low, $\Sigma_{b_1^2}$ = low
2) α = low, $\Sigma_{b_1^2}$ = high
3) α = high, $\Sigma_{b_1^2}$ = low
4) α = high, $\Sigma_{b_1^2}$ = high

Conclusion

- The **overall treatment effect** in joint model is a combination of the treatment effect in the longitudinal and survival model
- The obtained treatment effect has a **Subject-Specific** interpretation
- Whether Subject-Specific or marginal effects are desirable depends on the target of inference
- A **marginal** overall treatment effect can be obtained using the proposed method

References

Hedeker et al. (2017)
A note on marginalization of regression parameters from mixed models of binary outcomes.
Biometrics 74(1), 354 – 361.

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Joint models for longitudinal and time-to-event data: With applications in R.
Chapman and Hall/CRC.

Thank you!