Methods for multi-stage designs with survival data and informative censoring

GRBIO retreat

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UNIVERSITAT POLITÈCNICA DE CATALUNYA BARCELONATECH
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UNIÓN EUROPEA FONDO EUROPEO DE DESARROLLO REGIONAL "Una manera de hacer Europa"
AGENCIA ESTATAL DE INVESTIGACIÓN

PhD thesis

- Within the SAFARI project
- Started in April 1st, 2025
- Co-supervised by Marta Bofill Roig and Werner Brannath (UniBremen)
- Clinical trials, survival analysis, adaptive designs


First, some notation

- T : Time to event
- $A \in \{0, 1\}$: Treatment group indicator, $A = 1$ denotes treatment and $A = 0$ denotes control
- $Z \in \{0, 1\}$: Baseline covariate of interest, e.g., a biomarker

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- $S_j(t)$: Survival function for each treatment $A = j$, for $j = 0, 1$
- τ : A given time of interest

- $\int_0^\tau S(t)\mathrm{d}t$: Restricted mean survival time (RMST)

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Marginal treatment effect

$$\int_0^\tau S_1(t)\mathrm{d}t - \int_0^\tau S_0(t)\mathrm{d}t,$$

i.e., we are interested in the difference of restricted mean survival times.

Let's simplify and clarify a bit

Consider the RMST directly as $\mathbb{E}(T)$:

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We are interested in **adjusting for the covariate** Z.

We can think of two different measures of the treatment effect adjusting for Z:

1. $$\mathbb{E}(T \mid Z = z, A = 1) - \mathbb{E}(T \mid Z = z, A = 0),$$

   e.g., using the coefficient of the treatment variable A in a Cox model that includes Z and A $\rightsquigarrow$ conditional effect

2. $$\mathbb{E}_Z\left[\mathbb{E}(T \mid Z, A = 1)\right] - \mathbb{E}_Z\left[\mathbb{E}(T \mid Z, A = 0)\right],$$

   the average treatment effect, averaging over the covariate Z $\rightsquigarrow$ **marginal effect**

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A brief reminder on sample size

To calculate the sample size needed for a clinical trial, we need to anticipate:

1. α level
2. Power $1 - \beta$
3. Treatment effect
4. Variance of the treatment effect estimator

How do we compute the sample size for the marginal treatment effect?

We need to obtain estimates for the **marginal treatment effect** and its corresponding **variance**.

1. Calculating the sample size accounting for an analysis that does not adjust for covariates[1]:

$$\mathbb{E}(T \mid A = 1) - \mathbb{E}(T \mid A = 0)$$

2. Calculating the sample size accounting for an analysis that adjusts for the covariate Z:

$$\mathbb{E}_Z \left[\mathbb{E}(T \mid Z, A = 1)\right] - \mathbb{E}_Z \left[\mathbb{E}(T \mid Z, A = 0)\right]$$

[1] FDA guideline (2023). Adjusting for covariates in randomized clinical trials for drugs and biological products: Guidance for industry

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First objective of the thesis

Approach to calculate the sample size in survival trials targeting a marginal effect adjusting for a covariate.

[1] FDA guideline (2023). Adjusting for covariates in randomized clinical trials for drugs and biological products: Guidance for industry

Estimation of the marginal treatment effect adding the covariate (I/II)

We want to estimate the adjusted marginal treatment effect:

$$\Delta_Z = \int_0^\tau S_{1,Z}(t)\mathrm{d}t - \int_0^\tau S_{0,Z}(t)\mathrm{d}t$$

We estimate the covariate-averaged survivals:

$$\hat{\Delta}_Z = \int_0^\tau \hat{S}_{1,Z}(t)\mathrm{d}t - \int_0^\tau \hat{S}_{0,Z}(t)\mathrm{d}t$$

- For such estimators we use the fact that $S(t) = e^{-\Lambda(t)}$
- $\hat{S}_{j,Z}(t) = e^{-\hat{\Lambda}_{j,Z}(t)}$, where $\hat{\Lambda}_{j,Z}(t)$ is an estimator of the marginal cumulative risk functions (next slide)

Estimation of the marginal treatment effect adding the covariate (II/II)

The estimator $\hat{\Lambda}_{j,Z}(t)$ that we plan to use is a doubly robust estimator [2]:

- It combines two estimating strategies:
  1. **Outcome model:** Treatment-stratified Cox model with the covariate
  2. **Treatment assignment model:** Inverse probability of treatment weighting (IPTW) using a logistic regression with the covariate
- Consistent if either of the two models is correctly specified

[2] Zhang and Schaubel (2012). "Contrasting treatment-specific survival using double-robust estimators". *Statistics in medicine* 31.30, pp. 4255–4268

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- Consistent if either of the two models is correctly specified ✓

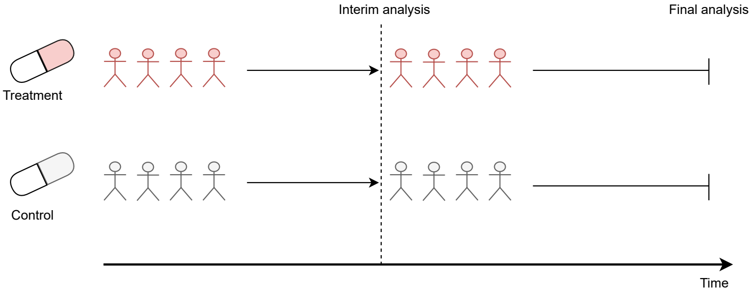
Variance of the marginal treatment effect estimator

$$\begin{aligned}\mathrm{Var}(\hat{\Delta}_Z) = &\ \text{IPTW model} + \text{Cox model Score and Fisher's information matrix}\\ &+ \text{Cox model distribution} + \text{Censoring distribution} + \text{Augmentation term}\end{aligned}$$

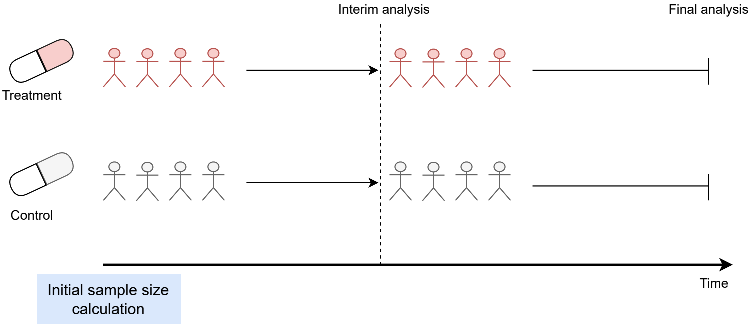
The terms depend on:

- Covariate distribution $\rightsquigarrow$ **unknown!**
- Censoring distribution $\rightsquigarrow$ **unknown!**

The proposal



The proposal



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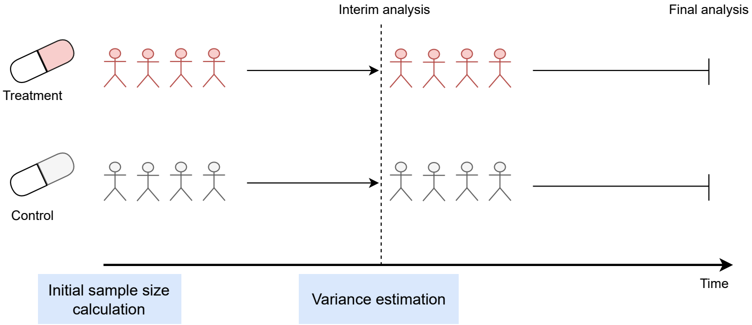

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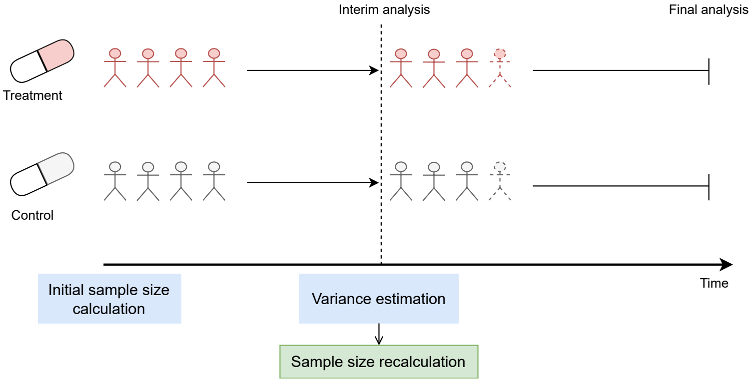

Next steps

- How can we estimate the different terms of the variance $\rightsquigarrow$ explore different variance estimators
- Which terms can be updated with a blinded approach
- Which terms can be updated with an unblinded approach

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- Which terms can be updated with an unblinded approach
- Keep reading and having fun! :)

References

FDA, U.S. *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products: Guidance for Industry*. Docket No. FDA-2019-D-0934. 2023.

Zhang, Min and Douglas E Schaubel. “Contrasting treatment-specific survival using double-robust estimators”. In: *Statistics in medicine* 31.30 (2012), pp. 4255–4268.

Zhao, Lihui et al. “On the restricted mean survival time curve in survival analysis”. In: *Biometrics* 72.1 (2016), pp. 215–221.

Thank you for your attention!

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