Combining Covariate Adjustment with Group Sequential and Information Adaptive Designs to Improve Randomized Trial Efficiency

UNIVERSITEIT GENT

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Joint work with

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Outline

Covariate Adjustment

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  - e.g., age, baseline severity and comorbidities

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- In many clinical trials, data is collected on different **patient characteristics** at the time of entry
  - e.g., age, baseline severity and comorbidities
- **Covariate adjustment** is a statistical analysis method with high potential to **improve precision** for many of these trials.
  - **Pre-planned** adjustment for baseline variables when estimating **average treatment effect**.
  - Estimand is same as when using unadjusted estimator (e.g., difference in means).
  - **Goal**: avoid making any model assumptions beyond what's assumed for unadjusted estimator (**robustness to model misspecification**).

(e.g., Koch et al., 1998; Yang and Tsiatis, 2001; Rubin and van der Laan, 2008; Tsiatis et al., 2008; Moore and van der Laan, 2009b,a; Zhang, 2015; Jiang et al., 2018; Benkeser et al., 2020)

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- Estimator: G-computation/Standardization
  1. Fit logistic regression model for

$$P(Y=1|A,W) = logit^{-1}(\gamma_0 + \gamma_1 A + \gamma_2 W).$$

  2. Compute standardized estimators for treatment specific means
     - $\hat{E}(Y|A=1) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 + \hat{\gamma}_2 W_i)$
     - $\hat{E}(Y|A=0) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_2 W_i)$
  3. Calculate $\hat{\theta} = \hat{E}(Y|A=1) - \hat{E}(Y|A=0)$

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- Problematic:
  - Resulting analyses are **inefficient** by not fully exploiting the available information in the data,
  - thereby **forfeiting the opportunity to reduce the required sample size**.

Potential Obstacles Leading to Underutilization

1. Many covariate adjustment methods are **incompatible with 'standard' group sequential designs** (GSDs).
   - GSDs can **reduce the length** of a Phase 3 trial.
   - An obstacle for realizing precision gains from covariate adjustment as GSDs are commonly used for efficiency and ethical reasons.

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   - An obstacle for realizing precision gains from covariate adjustment as GSDs are commonly used for efficiency and ethical reasons.
2. The **uncertainty** at the design stage about the **amount of precision gain and corresponding sample size reduction**.
   - An incorrect projection of a covariate's prognostic value risks an over- or underpowered future trial.

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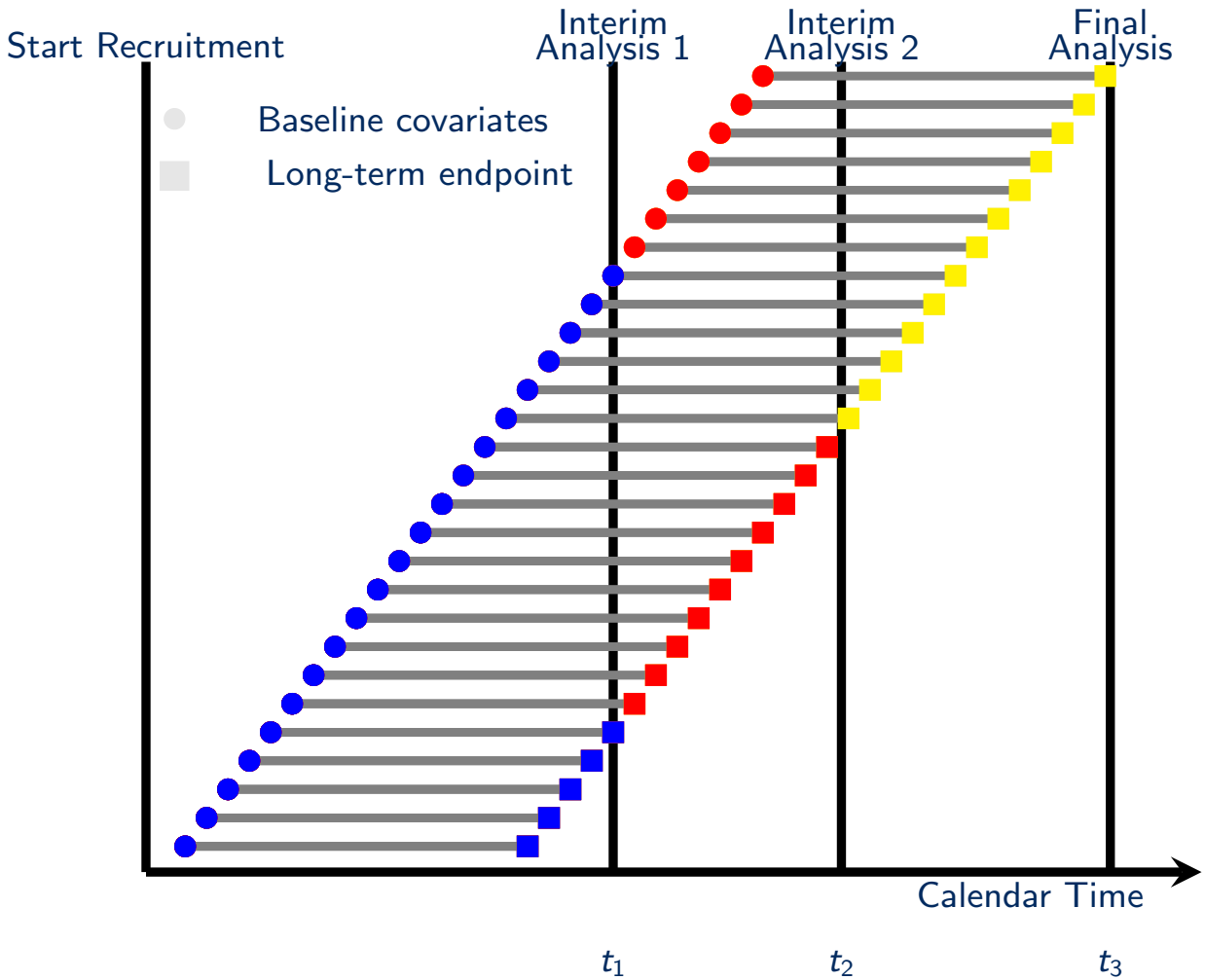

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    - Allow to stop early for efficacy and/or futility.
- Multiple looks at accumulating data **increase type I error**
  - Range of methods for defining the critical values for interim analyses.
    (Pocock, 1977; O'Brien and Fleming, 1979; Lan and DeMets, 1983)

Group Sequential Designs: Independent Increments

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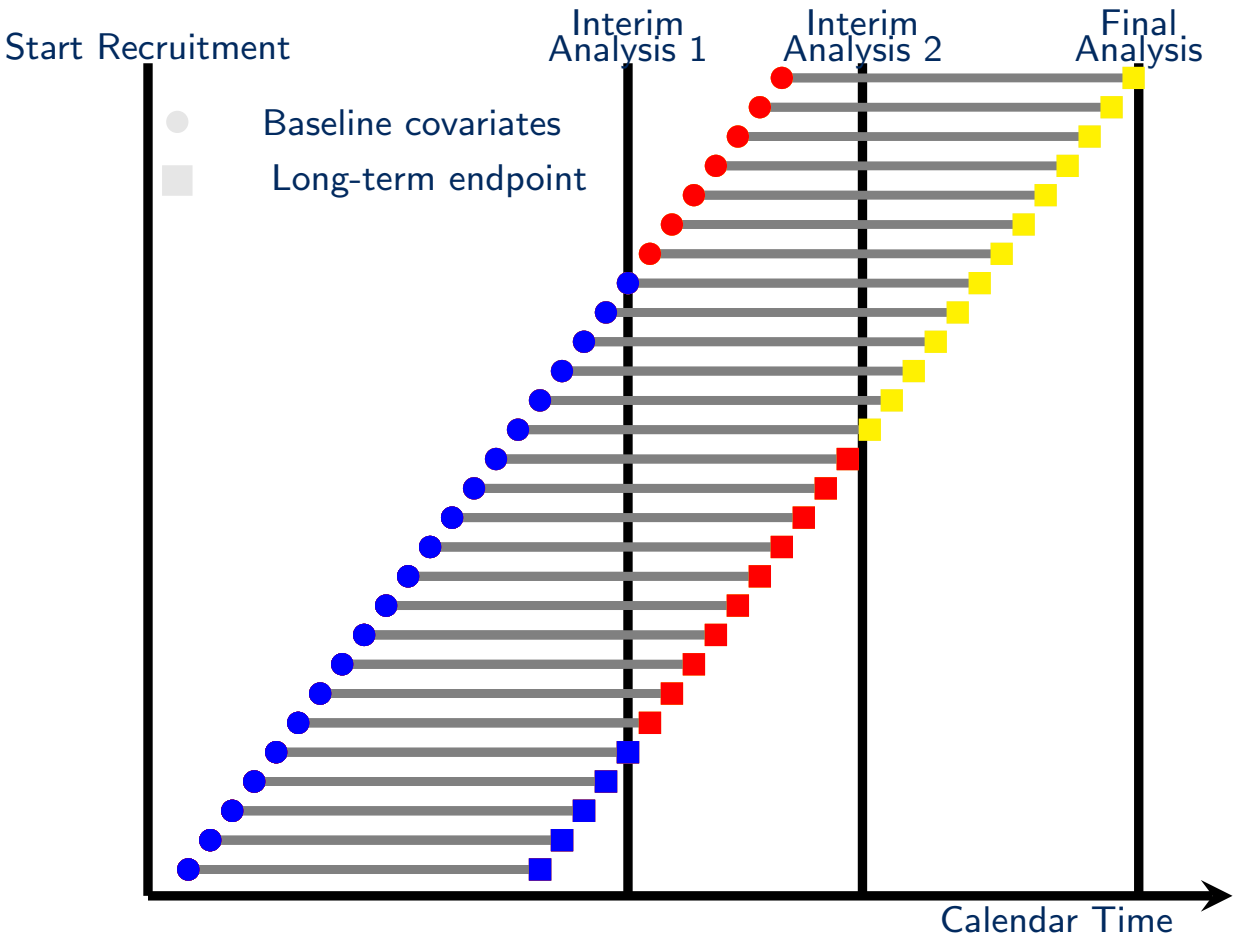

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- Proposal: **modifying** any RAL estimator so that it has the **independent increments property**.

Proposal: Motivation

- **Goal:** Obtain at each analysis time t_k an estimator $\widetilde{\theta}_{t_k}$ that
  1. is consistent for θ,
  2. is asymptotically linear,
  3. is asymptotically normal,
  4. is asymptotically as or more precise as the original estimator $\widehat{\theta}_{t_k}$, and
  5. has the independent increments property.

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  5. has the independent increments property.

- We will focus on finding the **linear combination**

$$\widehat{\theta}_{t_k} - \sum_{k'=1}^{k-1} \lambda_{k'}^{(k)} (\widehat{\theta}_{t_k} - \widehat{\theta}_{t_{k'}})$$

  with **minimal variance**.

Proposal

- At $k = 1$, we let $\tilde{\theta}_{t_1} = \hat{\theta}_{t_1}$ and $\tilde{Z}_1 = Z_1 = \frac{\hat{\theta}_{t_1} - \theta_0}{\widehat{se}(\hat{\theta}_{t_1})}$.

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Algorithm for Analysis Timing: Design Stage

- Specify the operating characteristics of the study

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- We **compute the maximum/total information** needed to preserve these operational characteristics

$$\left(\frac{z_{\alpha/2} + z_{\beta}}{\theta_A - \theta_0}\right)^2,$$

for a fixed design (no interim analyses), and

$$\left(\frac{z_{\alpha/2} + z_{\beta}}{\theta_A - \theta_0}\right)^2 IF$$

when data is sequentially monitored with the possibility of early stopping.

(Mehta and Tsiatis, 2001)

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- We consider a trial with an interim analysis when 50% of the information is available:
  - We conduct the interim analysis at time t_1 when

$$(\widehat{se}(\hat{\theta}_{t_1}))^{-2} \geq 0.5 \cdot \left(\frac{z_{\alpha/2} + z_{\beta}}{\theta_A - \theta_0} \right)^2 IF.$$

  - We conduct the final analysis at time t_2 when

$$(\widehat{se}(\hat{\theta}_{t_2}))^{-2} \geq \left(\frac{z_{\alpha/2} + z_{\beta}}{\theta_A - \theta_0} \right)^2 IF.$$

(Mehta and Tsiatis, 2001; Zhang, 2009)

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MISTIE III trial (Stroke)

- Functional outcome: proportion of patients who achieved a modified Rankin Scale score of 0-3 at 365 days (**binary**).
- Estimand of interest: **risk difference**.
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- We will focus on information instead of sample size!

Simulation Study: $K = 2$

- We perform interim analysis when 50% of the (total) information is available
  - Total information: 648

		$\theta = 0.13$ (Alternative)		
		Power	**ASN**	AAT
Original estimators $\hat{\theta}_{t_k}$	Unadjusted	88.3%	**534**	1566
	Standardization	87.1%	**431**	1299
Orthogonalized estimators $\tilde{\theta}_{t_k}$	Standardization	87.0%	**431**	1299

ASN: average sample number; AAT: average analysis time (days).

Note: We did a small sample size correction for standardization estimator.

Conclusion under alternative:
19% reduction of sample size due to covariate adjustment

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		$\theta = 0$ (Null)		
		Type I	**ASN**	AAT
Original estimators $\hat{\theta}_{t_k}$	Unadjusted	5.29%	**628**	2014
	Standardization	5.06%	**449**	1542
Orthogonalized estimators $\tilde{\theta}_{t_k}$	Standardization	5.05%	**449**	1542

AAT: average analysis time (days); ASN: average sample number.

Note: We did a small sample size correction for standardization estimator.

Conclusion under null:
29% reduction of sample size due to covariate adjustment

Outline

Discussion

- We performed additional simulations under violation of independent increments property:

		Type I
Original estimators $\widehat{\theta}_{t_k}$	Standardization	5.37%
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- Simulations have only shown small deviations from independent increment structure.

- In practice, underlying **data-generating mechanism is unknown**.

- **Safer** to use the proposal as it guarantees to maintain the Type I error in large samples.

Discussion

Importantly, works for **all kind of endpoints and estimands** as long as the considered estimators are **consistent for θ and asymptotically linear**.
(**Not necessarily covariate adjusted estimators!**).

Thank you for your attention!

Interested? https://doi.org/10.48550/arXiv.2201.12921

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The opinions in this presentation are of the author and do not necessarily represent those of anyone else.

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Proposal: Variance

- Estimate the variance of $\widetilde{\theta}_{t_k}$ as

$$\widehat{se}(\widetilde{\theta}_k)^2 = (-(\widehat{\boldsymbol{\lambda}}^{(k)})^t, 1)\widehat{Cov}\left((\hat{\theta}_{t_k} - \hat{\theta}_{t_1}, \ldots, \hat{\theta}_{t_k} - \hat{\theta}_{t_{k-1}}, \hat{\theta}_{t_k})^t\right)(-(\widehat{\boldsymbol{\lambda}}^{(k)})^t, 1)^t.$$

- $n \cdot \widehat{se}(\widetilde{\theta}_k)^2$ is a **consistent** estimate for the asymptotic variance $n \cdot Var(\widetilde{\theta}_{t_k})$.
- This guarantees **asymptotically correct hypothesis testing and confidence intervals**.

Algorithm for Analysis Timing: (Dis)advantages

- The **information-adaptive design** is well suited for being adopted for covariate adjusted estimators:
  - We do **not have to prespecify the prognostic value of the covariates** nor other nuisance parameters.
  - When the estimator is more efficient than unadjusted estimator, covariate adjustment can lead to a **shorter trial** due to faster information accrual.

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  - When the estimator is more efficient than unadjusted estimator, covariate adjustment can lead to a **shorter trial** due to faster information accrual.
- **Administrative inconvenience**: it does not give an idea to the investigators about the necessary resources (i.e., length of study, sample size, ...).
  - We suggest to posit some **guesses on the nuisance parameters**, and
  - use the **emerging data to evaluate** whether the maximum information can be reached with the available resources.