

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

Planning

- 1 Background, Problem Setting and Set Up
- 2 Proposal: Combining Covariate Adjustment and GSDs
- 3 Proposal: Combining Covariate Adjustment and Information-Adaptive Designs
- 4 Simulation Study
- 5 Discussion

Outline

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Covariate Adjustment

- **Covariate adjustment** is a statistical analysis method with high potential to **improve precision** for many 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)

Group Sequential Designs

- A commonly used type of clinical trial design that involves **pre-planned interim analyses**
 - where the trial can be **stopped early** for efficacy or futility.
- Prevalent in confirmatory clinical trials for **ethical and efficiency reasons** as they potentially **save time and resources** by allowing early termination of the trial.

Problem Setting

- **Combination** of covariate adjustment and group sequential designs has the **potential to offer the benefits of both methods**:
 - using covariate adjusted estimators at interim and final analyses of a group sequential design.
- Several **challenges** involved in combining these two approaches.

Potential Challenges

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 - This is the case when models used to construct the estimators are misspecified.
- 2 The **uncertainty** at the design stage about the **amount of precision gain and corresponding sample size reduction**.
 - Proposals have been made to use external trial data to estimate the precision gain.
 - Nevertheless, an incorrect projection of a covariate's prognostic value risks an over- or underpowered future trial.
 - This is also an obstacle in trials without interim analyses.

Endpoints, Estimands and Estimators

- The proposal works for **all types of common outcomes**
 - e.g., continuous, binary, ordinal, and time-to-event
- The proposal accommodates **any estimand**, including
 - risk difference, relative risk and odds ratio for binary outcomes,
 - difference in restricted mean survival times and relative risk for time-to-event outcomes,
 - ...
- The proposal will be applicable to **any (adjusted and unadjusted) estimator** as long as it is regular and asymptotically linear (RAL) and consistent for the estimand of interest.
 - e.g., *G-computation* estimator (as suggested in the recent FDA draft guidance on covariate adjustment)

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- Estimator: G-computation/Standardization

1 Fit logistic regression model for

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

2 Compute standardized estimators for treatment specific means

- $\hat{E}(Y|A = 1) = \frac{1}{n} \sum_{i=1}^n \text{logit}^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 + \hat{\gamma}_2 B_i)$

- $\hat{E}(Y|A = 0) = \frac{1}{n} \sum_{i=1}^n \text{logit}^{-1}(\hat{\gamma}_0 + \hat{\gamma}_2 B_i)$

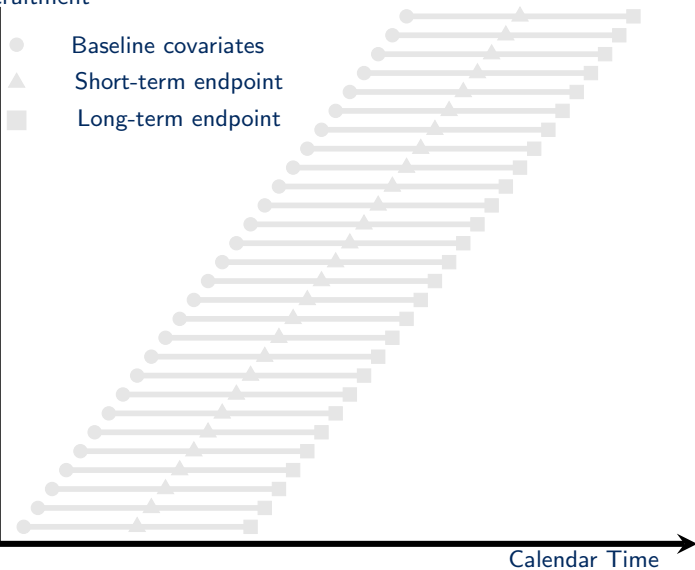
3 Calculate $\hat{\theta} = \hat{E}(Y|A = 1) - \hat{E}(Y|A = 0)$

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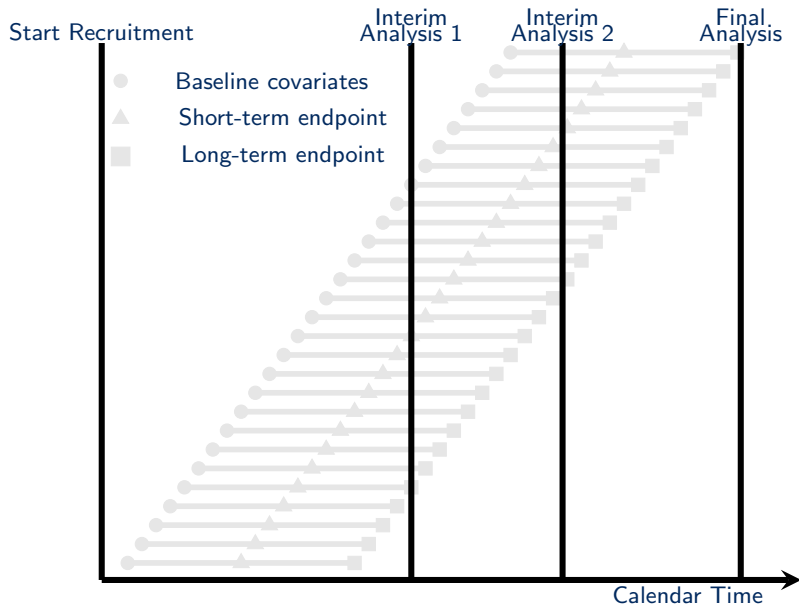
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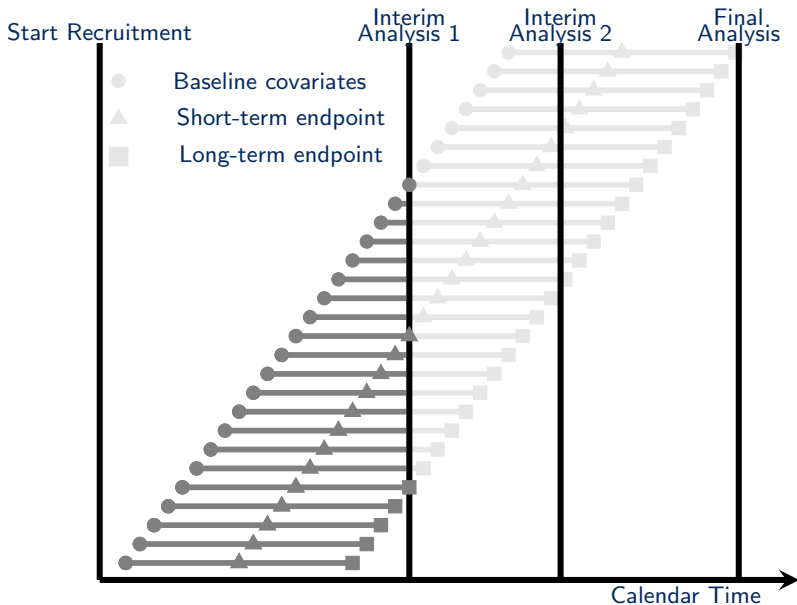
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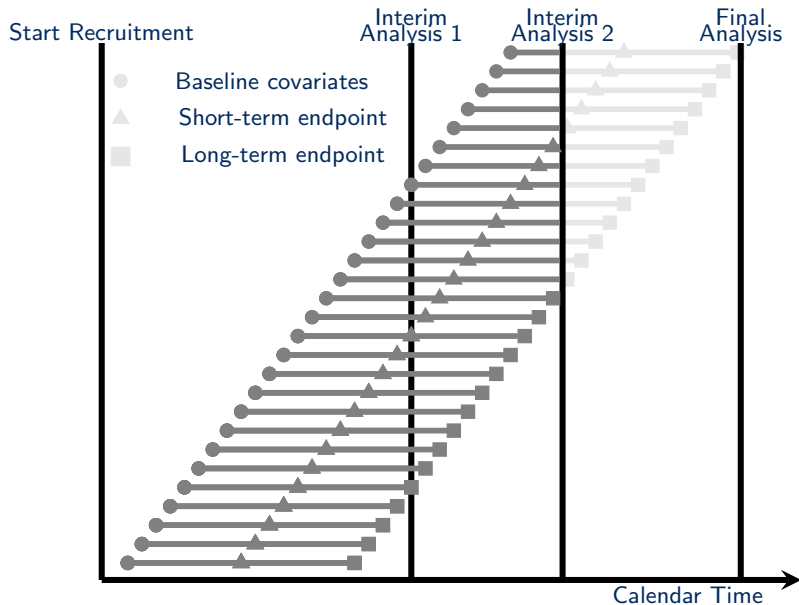
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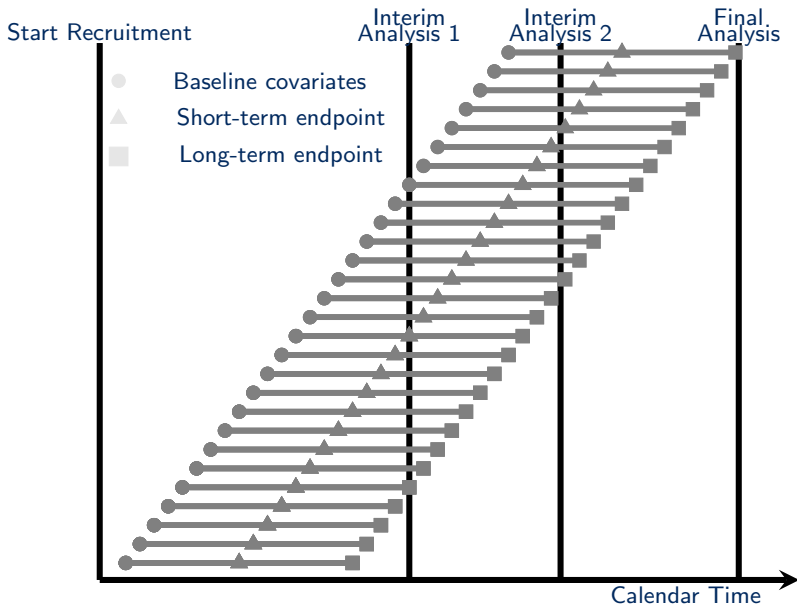
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in all n' recruited patients.

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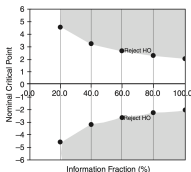
Group Sequential Design

- A group sequential design can **reduce the length** of a Phase 3 trial
 - Reaching a conclusion sooner (Stopping for efficacy/futility)
 - Faster access to effective treatments
 - Faster dropping of ineffective/harmful treatment
 - **Saving resources**

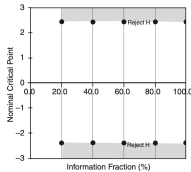
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 - Multiple looks at accumulating data **increase type I error**
 - Lower significant thresholds needs to be used for the interim analyses.
 - There are a range of methods for defining the critical values for interim analyses.
- (Pocock, 1977; O'Brien and Fleming, 1979; Lan and DeMets, 1983)

Group Sequential Designs: Popular Boundaries



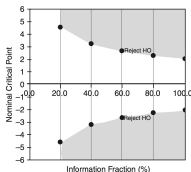
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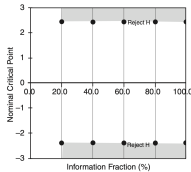
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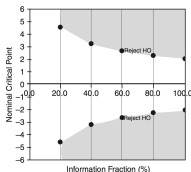
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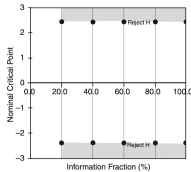
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- Boundaries depend on: **Information** accrued at the corresponding analysis times t_k ($k = 1, \dots, K$)
 - Defined as the reciprocal of the (interim) estimator's variance.
 - This is estimated by $\hat{\mathcal{I}}_k = (\hat{se}(\hat{\theta}_{t_k}))^{-2}$ for which we assume that $\lim_{n \rightarrow \infty} \hat{\mathcal{I}}_k / n = \lim_{n \rightarrow \infty} \{n \text{Var}(\hat{\theta}_{t_k})\}^{-1} = \mathcal{I}_k^*$.

Independent Increments (1)

- Assume that

$$(Z_1, \dots, Z_K) \xrightarrow{\mathcal{D}} \mathcal{N}(\boldsymbol{\delta}, \boldsymbol{\Sigma}),$$

where the covariance matrix $\boldsymbol{\Sigma}$ can be consistently estimated and $\boldsymbol{\delta}$ equals $\mathbf{0}$ under the null hypothesis.

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- In order to apply standard group sequential methods, $\boldsymbol{\Sigma}$ should have the **independent increments structure**:

- Each diagonal element of $\boldsymbol{\Sigma}$ is equal to 1.

- The (k', k) th element of $\boldsymbol{\Sigma}$, where $k' \leq k$, is equal to $\sqrt{\mathcal{I}_{k'}^* / \mathcal{I}_k^*}$.

(Scharfstein et al., 1997; Jennison and Turnbull, 1997, 1999)

Independent Increments (2)

- This general theory also implies that the **score statistics** $S_k = Z_k \sqrt{\mathcal{I}_k^*}$ are multivariate normal with
 - $S_k \sim \mathcal{N}(\delta_k \sqrt{\mathcal{I}_k^*}, \mathcal{I}_k^*),$
 - $\text{Cov}(S_{k'} - S_{k'-1}, S_k - S_{k-1}) = 0$ for $k' \neq k.$

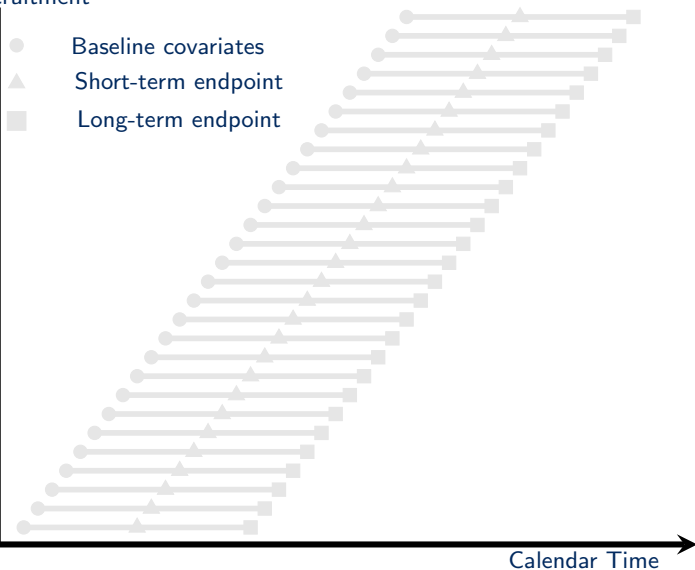
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- Thus, the score statistics have the **independent increments** property!

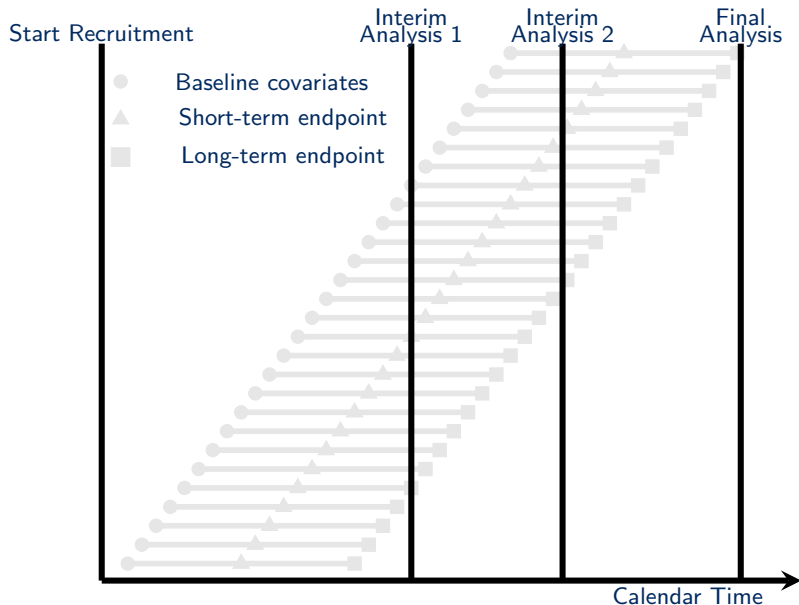
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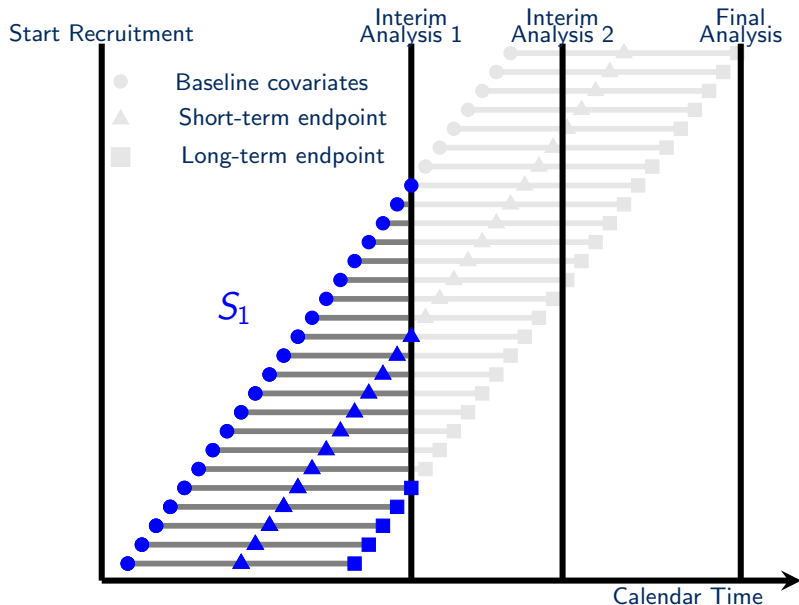
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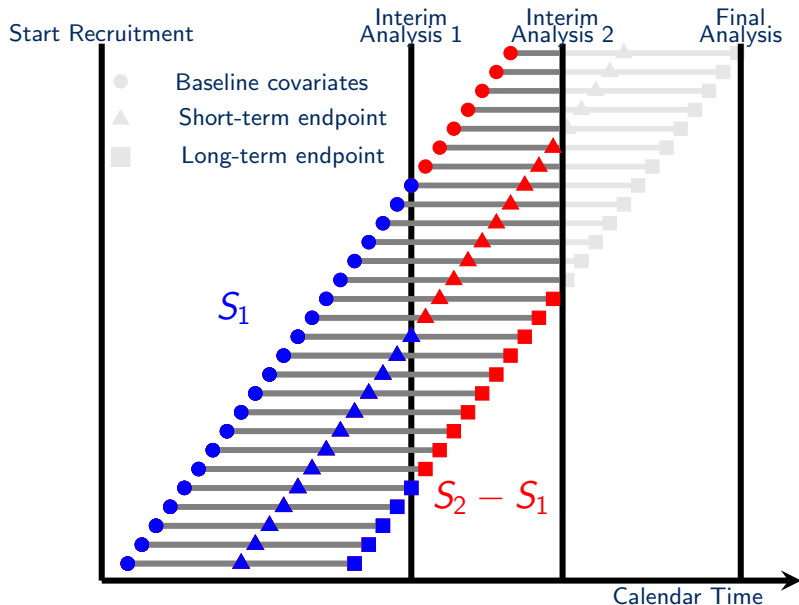
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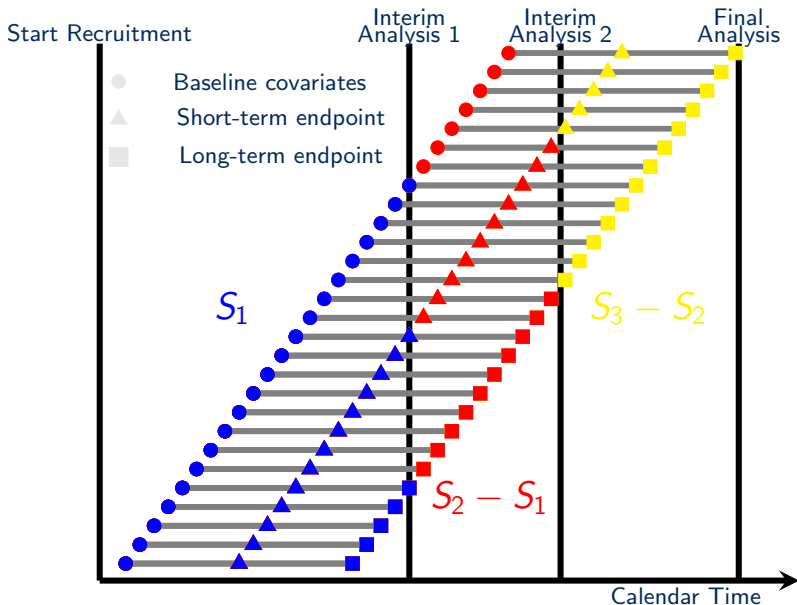
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- This property holds for

- (Difference in) sample means

- **Efficient estimators**

- ANCOVA with correctly specified model
 - G-computation and TMLE (if working models are correctly specified)
 - ...

(Scharfstein et al., 1997; Jennison and Turnbull, 1997, 1999)

Group Sequential Designs: Incompatibility

- Unfortunately, a sequence of RAL estimators $(\hat{\theta}_{t_1}, \dots, \hat{\theta}_{t_K})$ do not necessarily have the independent increments property.
- This was for example shown for:
 - Estimators based on generalized estimating equations (Shoben and Emerson, 2014)
 - G-computation and TMLE estimators when working models are misspecified (Rosenblum et al., 2015)
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 - A long list of further counterexamples is provided by Jennison and Turnbull (1997) and Kim and Tsiatis (2020)
- Proposal: **modifying** any RAL estimator so that it has the **independent increments property** and also has **equal or smaller variance than the original estimator**.

Proposal: Motivation

- **Goal:** Obtain at each analysis time t_k an estimator $\tilde{\theta}_{t_k}$ 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 $\hat{\theta}_{t_k}$, and
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■ We will focus on finding the **linear combination**

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

with **minimal variance**.

Proposal

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

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$$\left(\hat{\lambda}_1^{(k)}, \dots, \hat{\lambda}_{k-1}^{(k)}\right) = \arg \min_{(\lambda_1^{(k)}, \dots, \lambda_{k-1}^{(k)}) \in \mathbb{R}^{k-1}} \widehat{\text{Var}}\left\{\hat{\theta}_{t_k} - \sum_{k'=1}^{k-1} \lambda_{k'}^{(k)} (\hat{\theta}_{t_k} - \hat{\theta}_{t_{k'}})\right\},$$

$$\text{resulting in } \hat{\lambda}^{(k)} = \left\{ \widehat{\text{Var}} \left((\hat{\theta}_{t_k} - \hat{\theta}_{t_1}, \dots, \hat{\theta}_{t_k} - \hat{\theta}_{t_{k-1}})^t \right) \right\}^{-1} \\ \cdot \widehat{\text{Cov}} \left(\hat{\theta}_{t_k}, (\hat{\theta}_{t_k} - \hat{\theta}_{t_1}, \dots, \hat{\theta}_{t_k} - \hat{\theta}_{t_{k-1}})^t \right)$$

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Theorem: Asymptotic Properties

Consider any sequence of RAL estimators

$(\hat{\theta}_{t_1}, \dots, \hat{\theta}_{t_K})$ with all components consistent for θ , and for which

$$\lim_{n \rightarrow \infty} \hat{\mathcal{I}}_k / n = \lim_{n \rightarrow \infty} \left\{ n \widehat{\text{Var}}(\hat{\theta}_{t_k}) \right\}^{-1} = \lim_{n \rightarrow \infty} \left\{ n \text{Var}(\hat{\theta}_{t_k}) \right\}^{-1} = \mathcal{I}_k^* > 0,$$

and the covariance matrix Σ of the corresponding test statistics can be consistently estimated.

Then,

- the orthogonalized estimator sequence $(\tilde{\theta}_{t_1}, \dots, \tilde{\theta}_{t_K})$
 - also **RAL** with covariance matrix having the **independent increments property**,
- $\tilde{\theta}_{t_k}$ at each analysis time t_k
 - **consistent** estimator for θ
 - with **asymptotic variance less or equal to that of** $\hat{\theta}_{t_k}$.

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- 1 Many covariate adjustment methods are **incompatible with group sequential designs (GSDs)**.
 - Solved by modifying estimators through orthogonalization!
- 2 The **uncertainty** at the design stage about the **amount of precision gain and corresponding sample size reduction**.
 - The framework of GSDs affords us to be flexible on the sample size and focus on the statistical information.
 - We propose an “information-adaptive” trial design where the timing of the analyses is based on accruing information and is data adaptive.

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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.

Algorithm for Analysis Timing: Information

- We propose to **monitor the accrued information**, $(\widehat{se}(\hat{\theta}_t))^{-2}$, through time t .

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- We propose to **monitor the accrued information**, $(\widehat{se}(\hat{\theta}_t))^{-2}$, through time t .
- 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

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

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.

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.
- **Administrative inconvenience**: it does not give an idea to the investigators about the necessary resources (i.e., length of study, sample size, ...).

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 - Using the standard formulas for sample size calculations.
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- Assessing feasibility by **estimating the number of participants** corresponding with the maximum information.
 - Using the standard formulas for sample size calculations.
 - We recommend setting the **sample size conservatively** as if there were no precision gain from covariate adjustment.
- However, **miscalculations can occur** at the design stage.
 - We should use the **emerging data to evaluate** whether the maximum information will be reached in the planned time.

Obstacles Leading to Underutilization

- 1 Many covariate adjustment methods are **incompatible with group sequential designs** (GSDs).
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Obstacles Leading to Underutilization

- 1 Many covariate adjustment methods are **incompatible with group sequential designs** (GSDs).
 - Solved by modifying estimators through orthogonalization!
- 2 The **uncertainty** at the design stage about the **amount of precision gain and corresponding sample size reduction**.
 - Solved by using an “information-adaptive” trial design!

Outline

- 1 Background, Problem Setting and Set Up
- 2 Proposal: Combining Covariate Adjustment and GSDs
- 3 Proposal: Combining Covariate Adjustment and Information-Adaptive Designs
- 4 Simulation Study**
- 5 Discussion

MISTIE III trial (Stroke)

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

Simulation Study: $K = 1$

- **Information-adaptive design** with maximum information equal to 582
- **Maximum sample size design** with $n_{max} = 498$

		$\theta = 0.13$ (Alternative)			
		Power	ASN	AAT	AI
Information-adaptive design	Unadjusted	88.4%	571	1876	582
	Standardization	87.3%	433	1509	567
Maximum sample size design	Unadjusted	83.1%	-	1682	508
	Standardization	91.1%	-	1682	652

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

Conclusion under alternative:

24% reduction of sample size due to covariate adjustment

Simulation Study: $K = 1$

- **Information-adaptive design** with maximum information equal to 582
- **Maximum sample size design** with $n_{max} = 498$

		$\theta = 0$ (Null)			
		Type I	ASN	AAT	AI
Information-adaptive design	Unadjusted	5.28%	569	1871	582
	Standardization	5.28%	402	1427	568
Maximum sample size design	Unadjusted	5.14%	-	1682	509
	Standardization	5.14%	-	1682	705

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

Conclusion under null:

29% reduction of sample size due to covariate adjustment

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

Simulation Study: $K = 2$

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 - Total information: 648

		$\theta = 0$ (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

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Discussion

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

			Type I
Original estimators $\hat{\theta}_{t_k}$	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 and asymptotically linear (**Not necessarily covariate adjusted estimators!**).
- Our proposal will result in **faster, more efficient trials** for many disease areas, without sacrificing validity or power.
 - Can lead to faster trials even when the treatment is ineffective.

Discussion

- Importantly, works for **all kind of endpoints and estimands** as long as the considered estimators are consistent and asymptotically linear (**Not necessarily covariate adjusted estimators!**).
- Our proposal will result in **faster, more efficient trials** for many disease areas, without sacrificing validity or power.
 - Can lead to faster trials even when the treatment is ineffective.
- The approach can be extended to handle **stratified randomization** and **missing data** due to drop-out under MAR.



Thank you for your attention!

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

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Proposal: Variance

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

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

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