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

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Joint work with

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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

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

1. Many covariate adjustment methods are **incompatible with 'standard' group sequential designs** (GSDs).

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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

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

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

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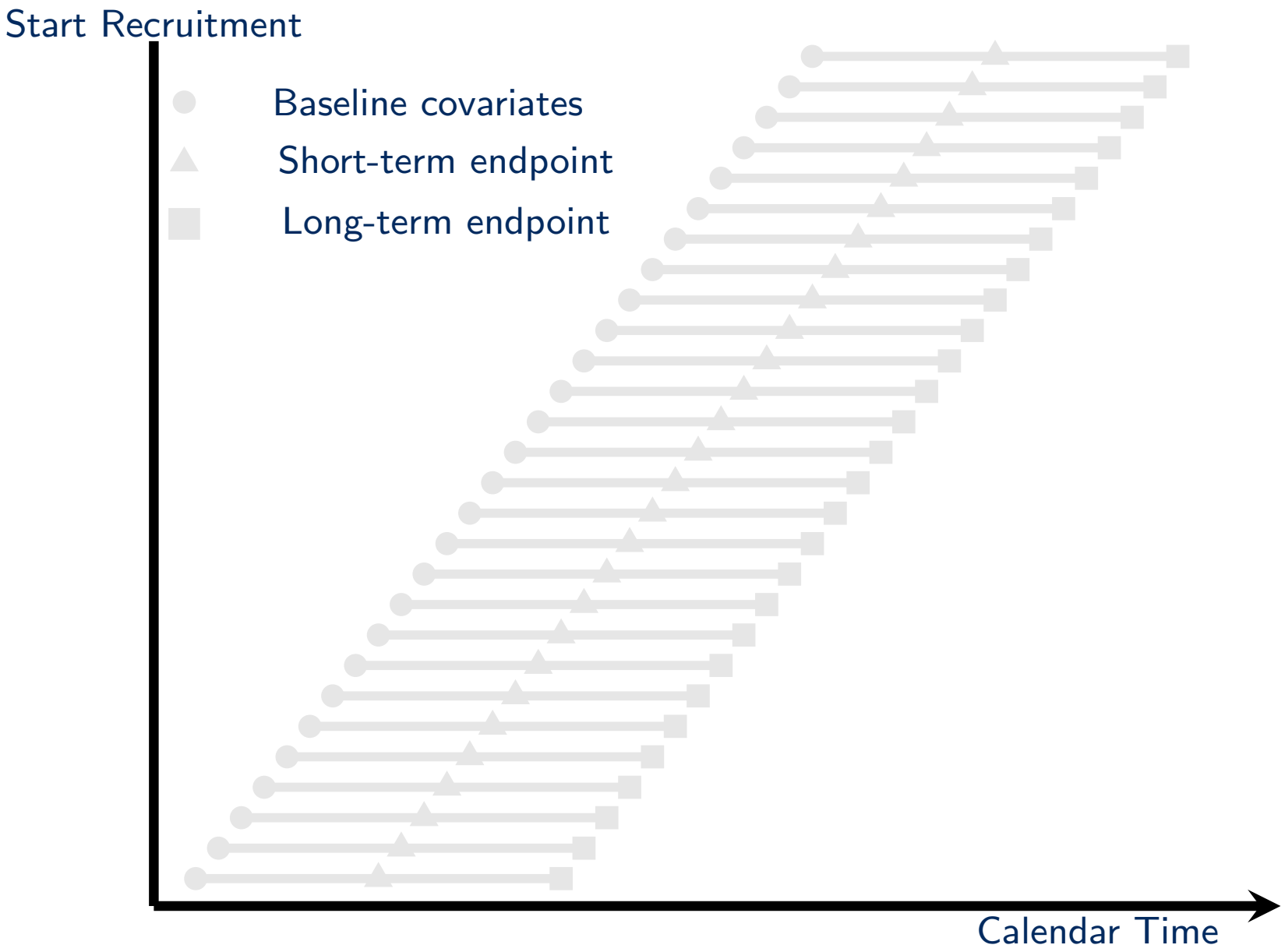

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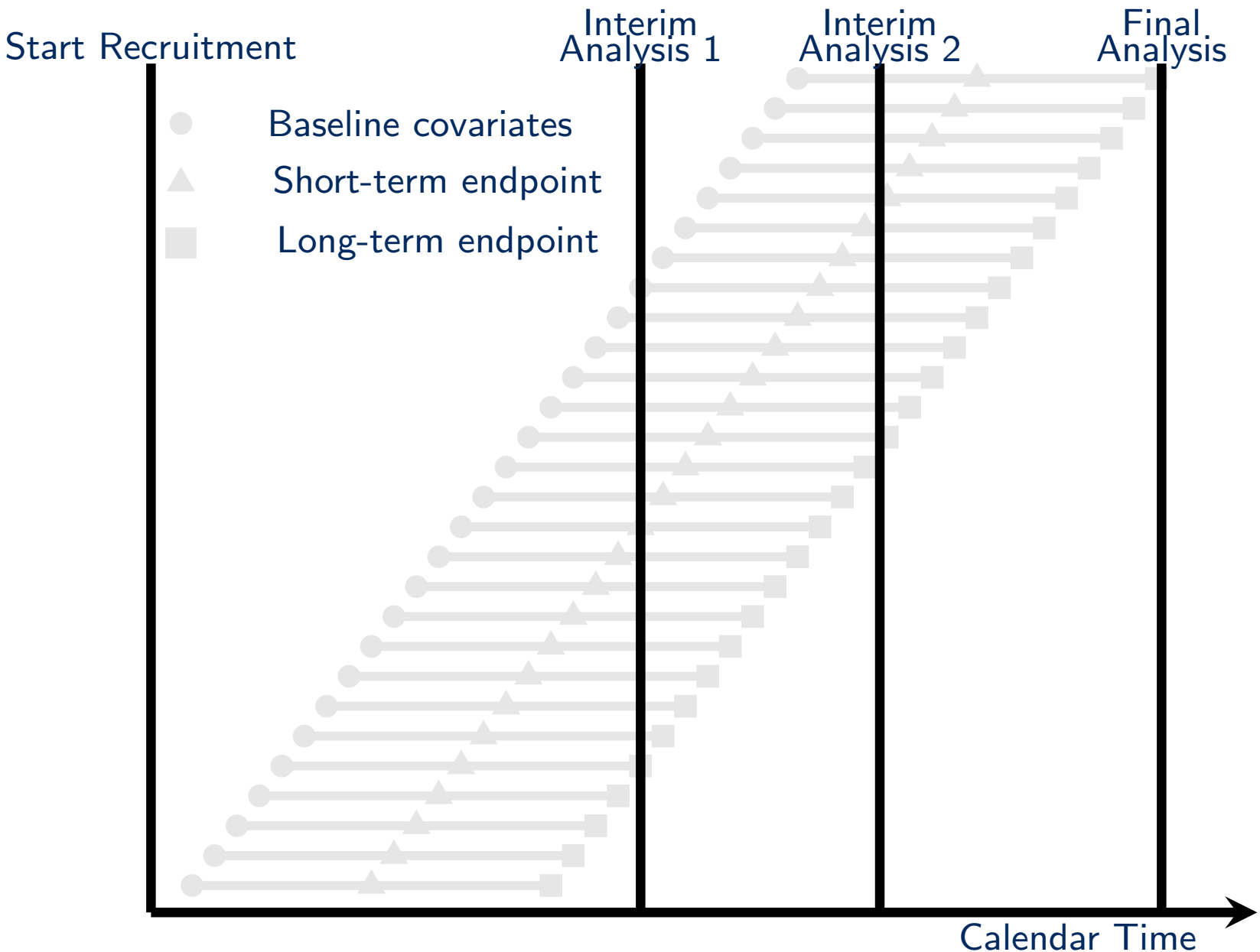

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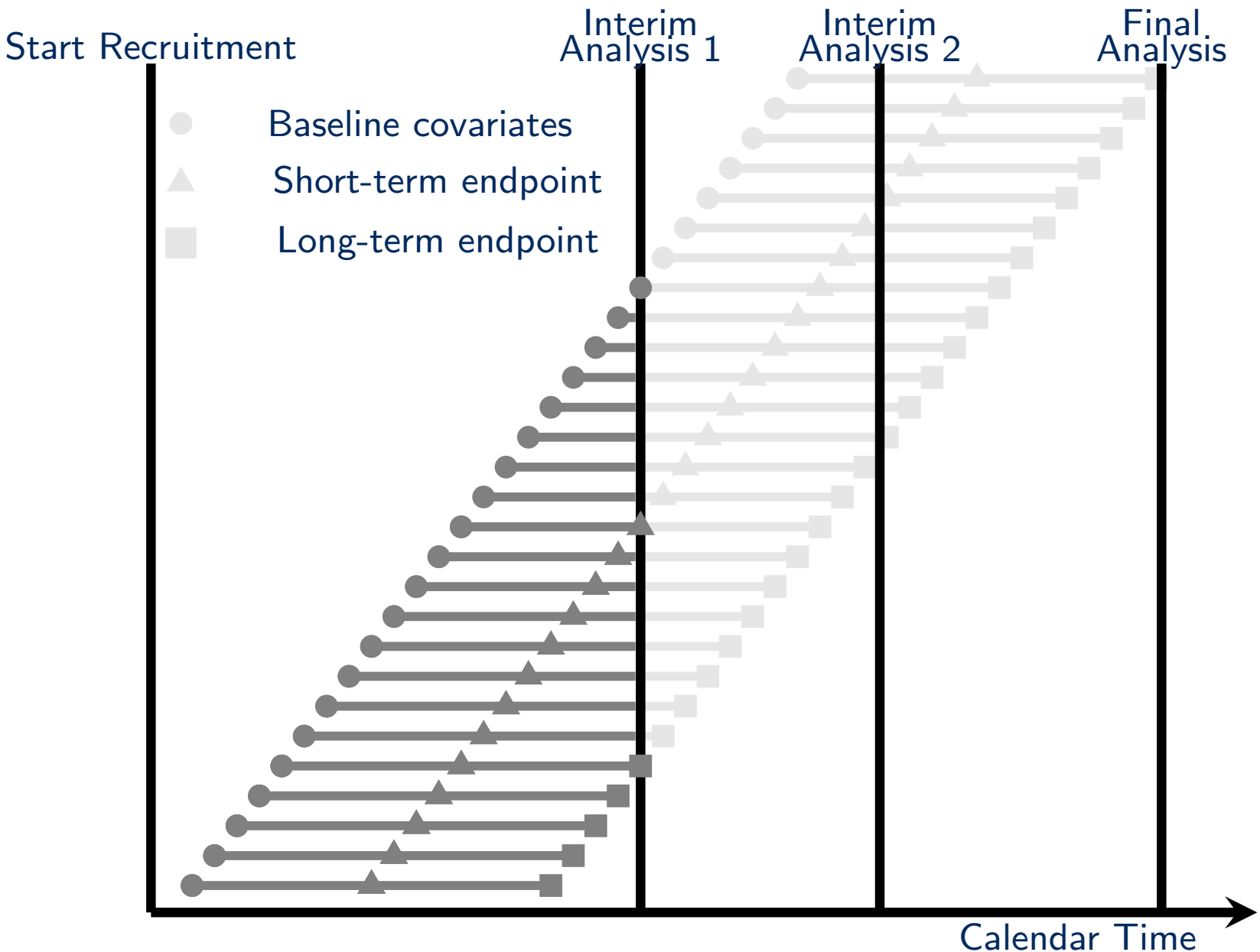

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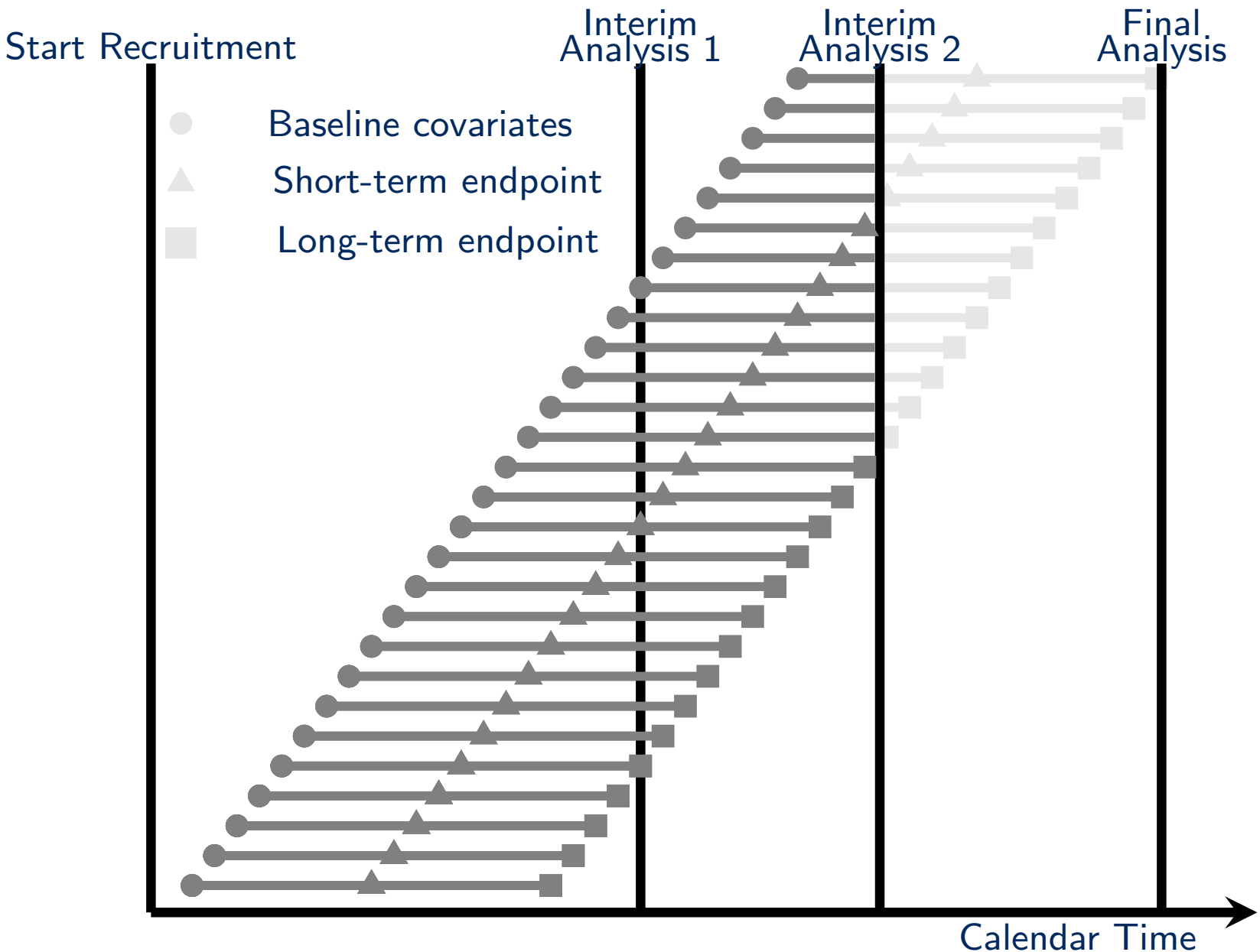

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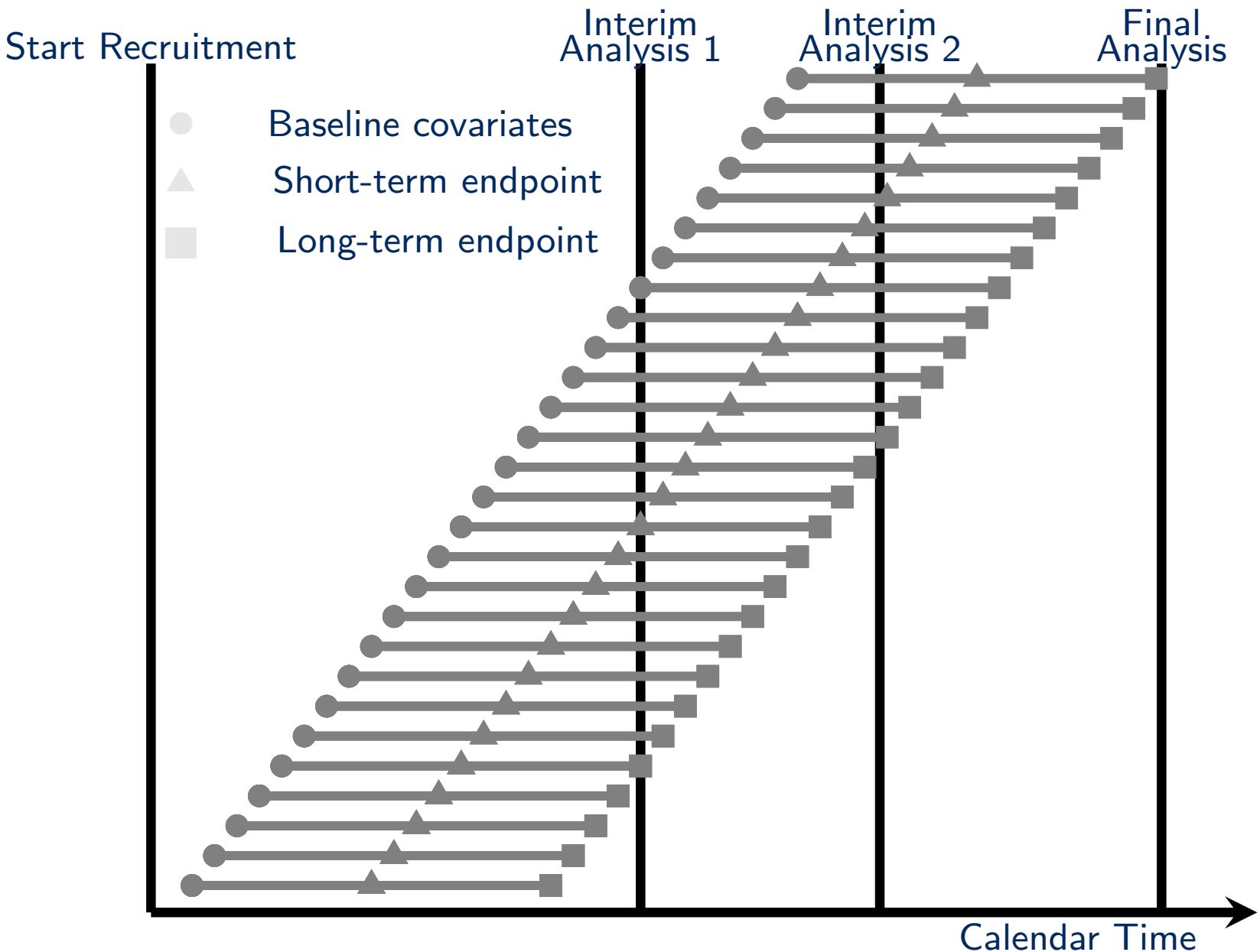

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Group Sequential Design

- 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
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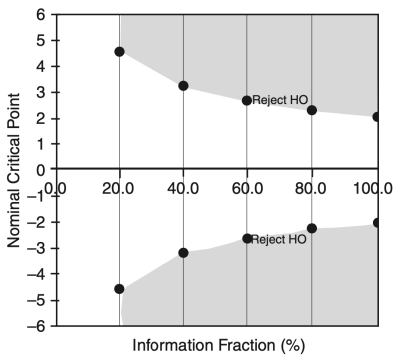
  - **Saving resources**
- Multiple looks at accumulating data **increase type I error**
  - Lower significant thresholds needs to be used for the interim analyses.
  - There are a range of methods for defining the critical values for interim analyses.

(Pocock, 1977; O'Brien and Fleming, 1979; Lan and DeMets, 1983)

Group Sequential Designs: Popular Boundaries



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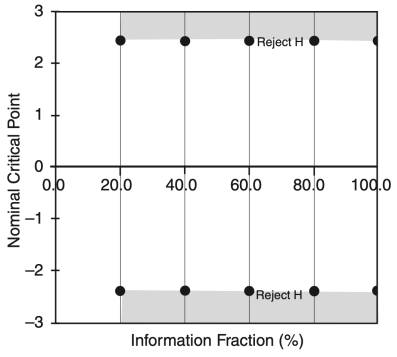

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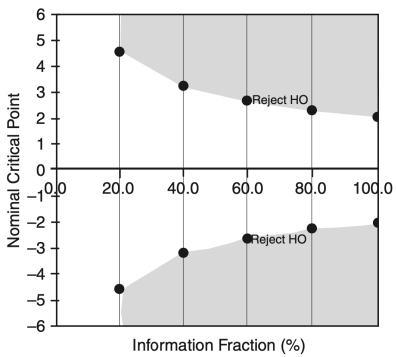

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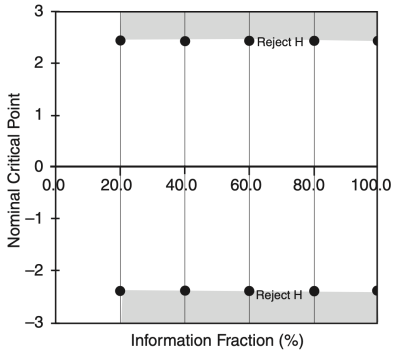

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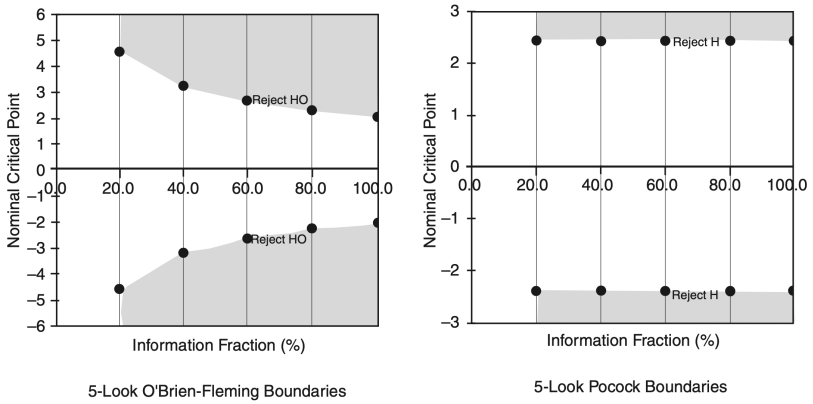

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  - Defined as the reciprocal of the (interim) estimator's variance.
  - This is estimated by $\hat{\mathcal{I}}_k = (\widehat{se}(\hat{\theta}_{t_k}))^{-2}$ for which we assume that $\lim_{n\to\infty} \hat{\mathcal{I}}_k/n = \lim_{n\to\infty} \left\{ nVar(\hat{\theta}_{t_k}) \right\}^{-1} = \mathcal{I}_k^*$.

Independent Increments (1)

- Assume that

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

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
  - $S_k \sim \mathcal{N}\left(\delta_k \sqrt{\mathcal{I}_k^*}, \mathcal{I}_k^*\right)$,
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- Thus, the score statistics have the **independent increments** property!

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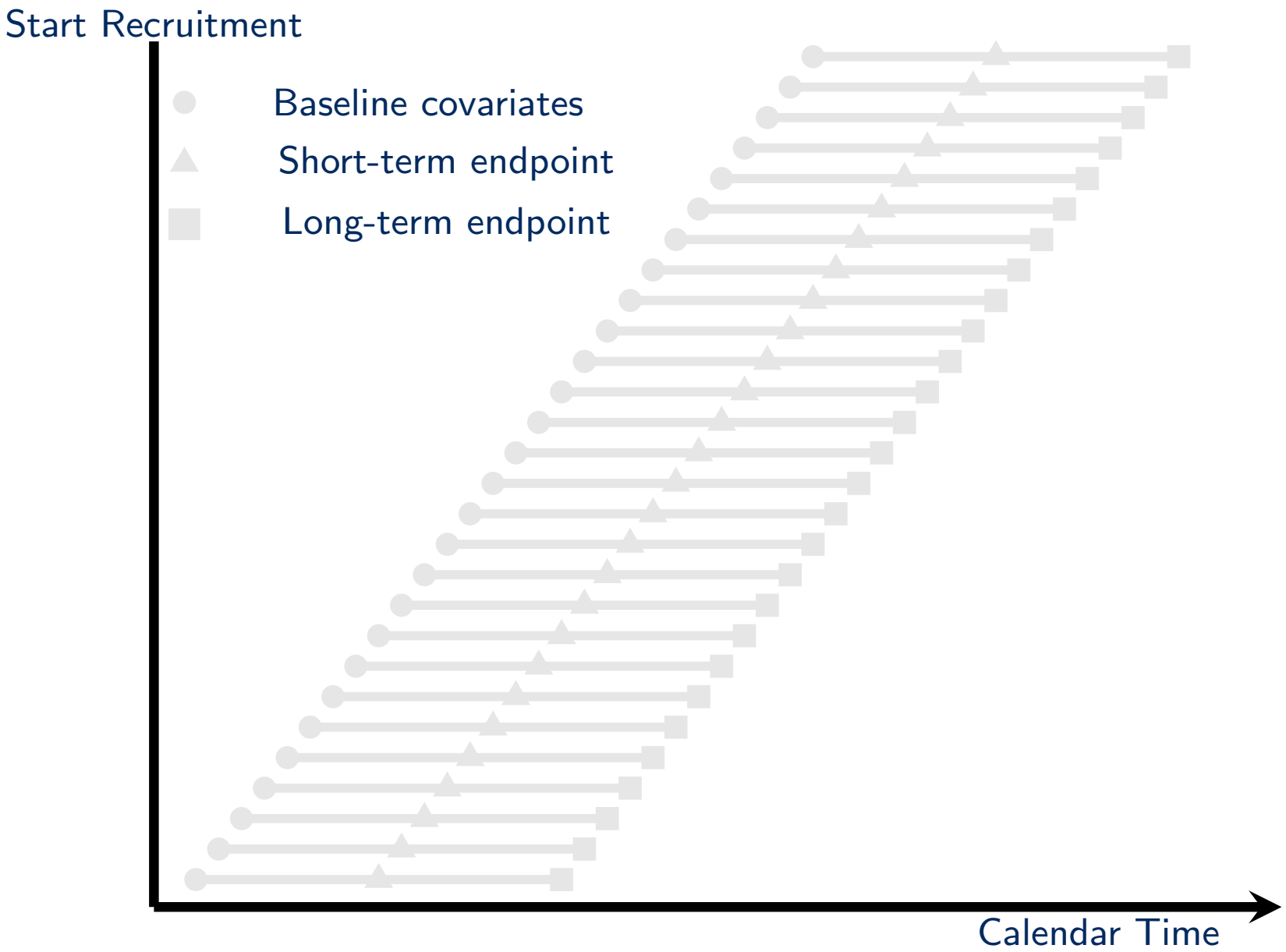

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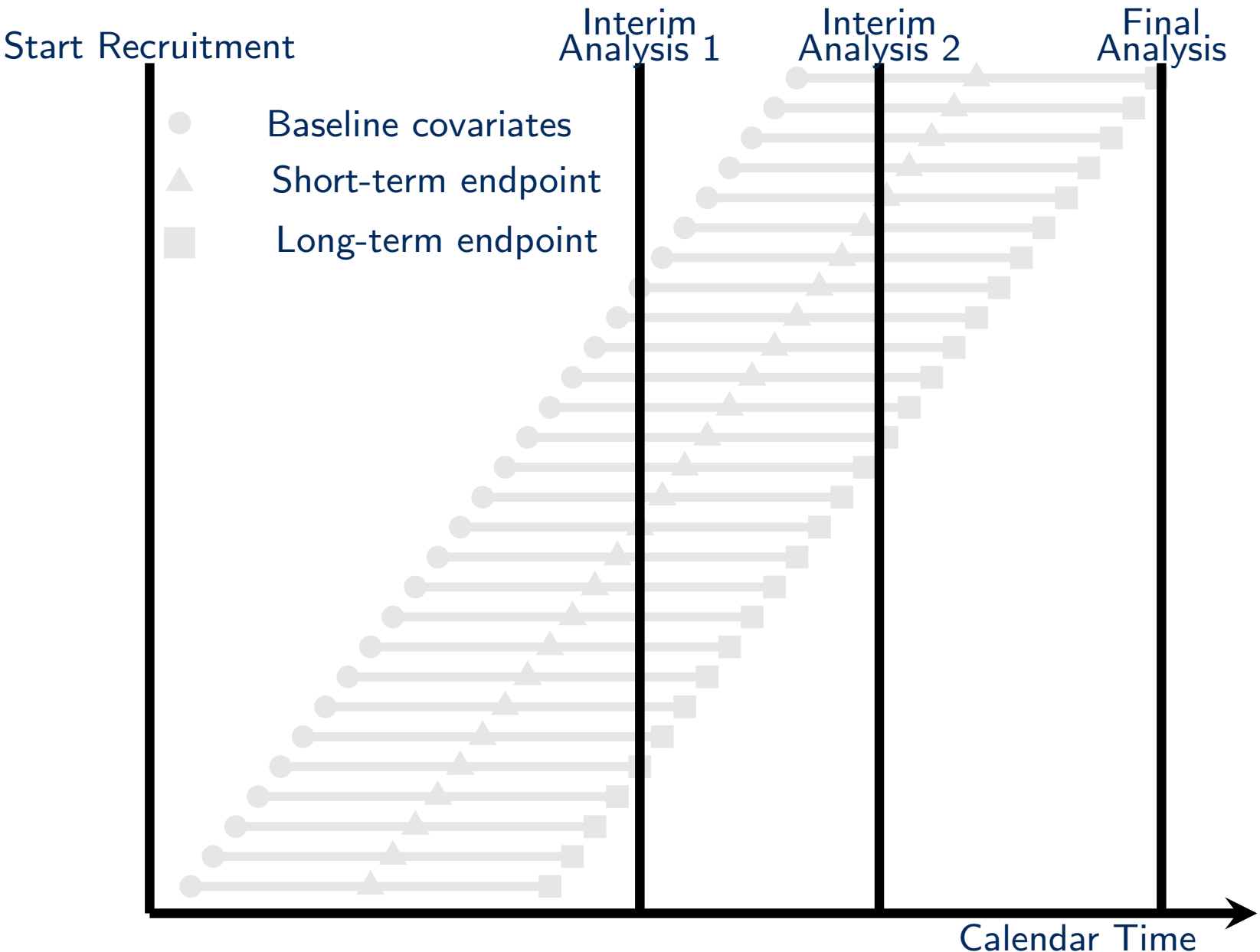

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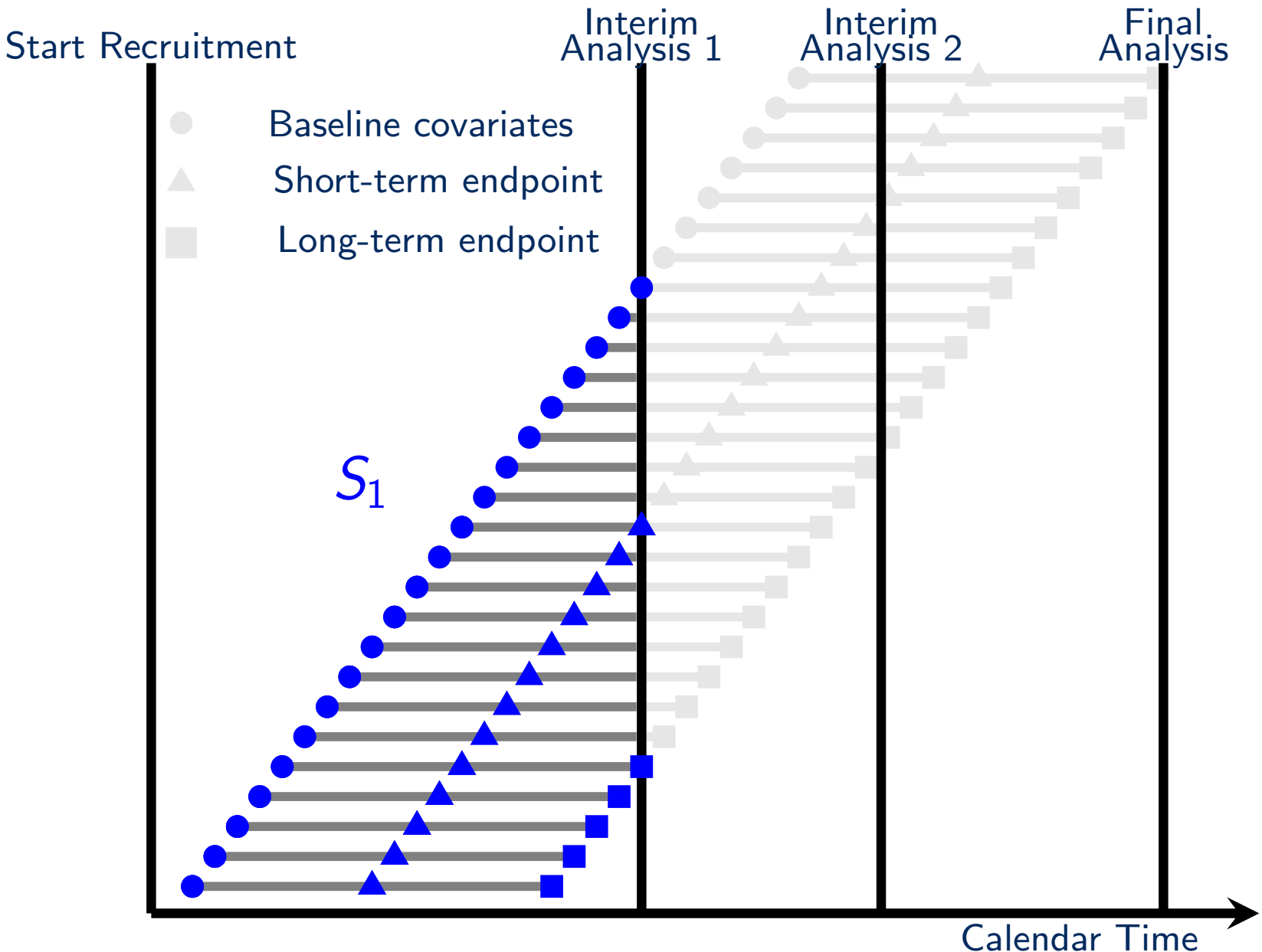

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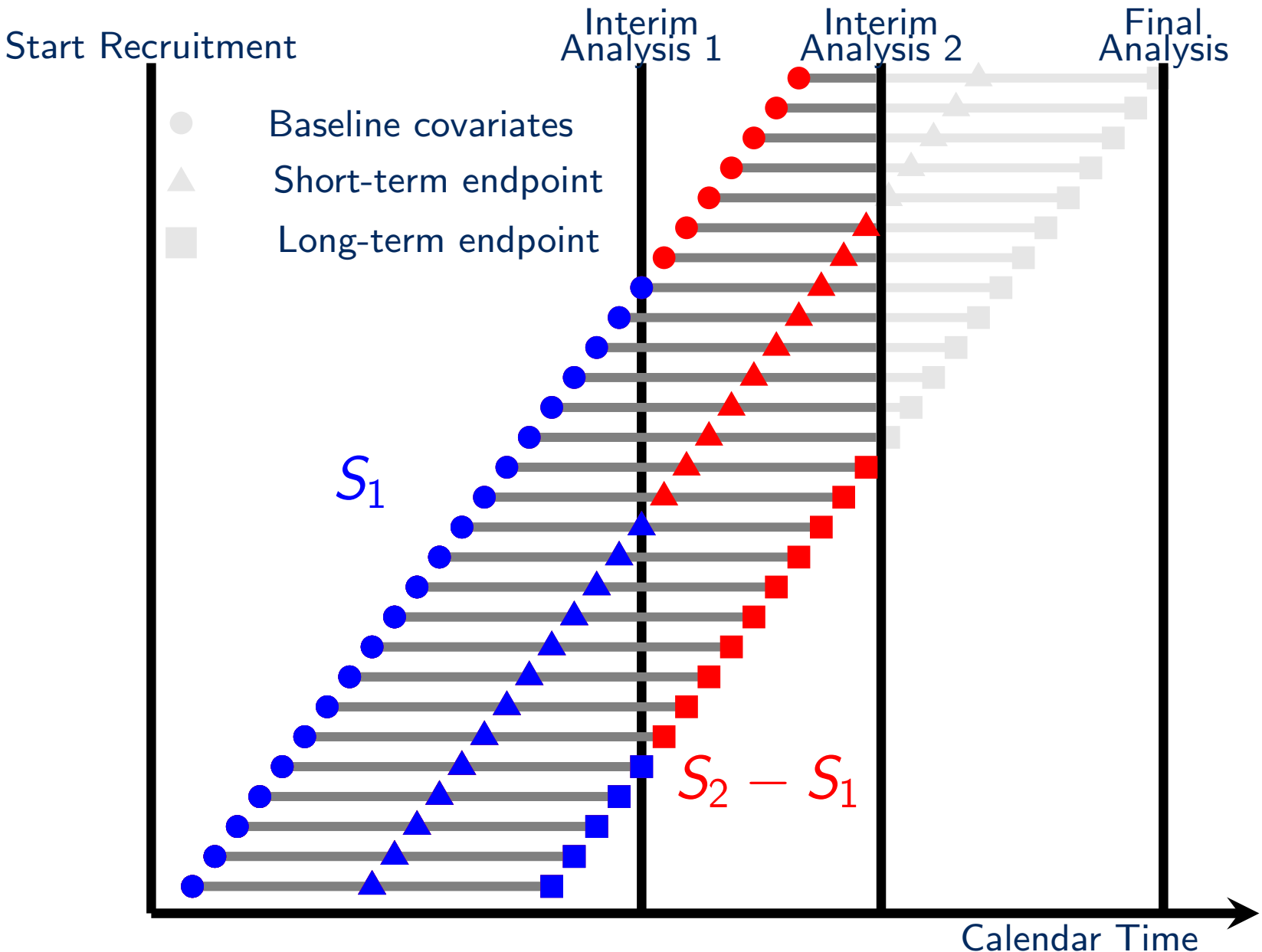

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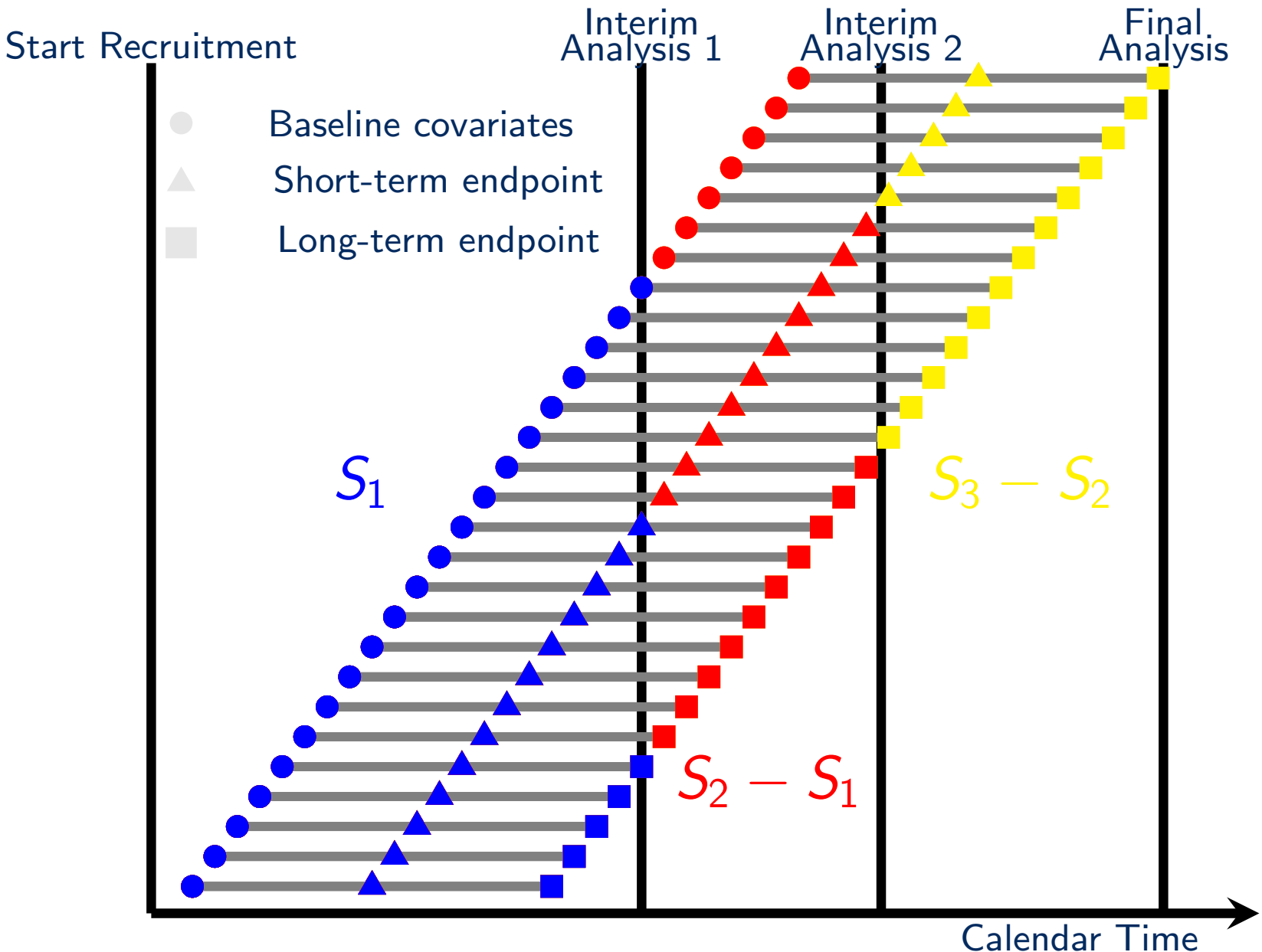

Independent Increments (4)

- On the estimator level, the general theory also implies that $\widehat{\theta}_{t_1}, \ldots \widehat{\theta}_{t_K}$ are asymptotically multivariate normal with
  - $\hat{\theta}_{t_k} \sim \mathcal{N}\left(\theta, (\mathcal{I}_k^*)^{-1}\right)$,
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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 $(\hat{\theta}_{t_1}, \ldots, \hat{\theta}_{t_K})$ 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 $\widetilde{\theta}_{t_k}$ that
  1. is consistent for θ,
  2. is asymptotically linear,
  3. is asymptotically normal,
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- 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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resulting in $\widehat{\boldsymbol{\lambda}}^{(k)} = \left\{\widehat{Var}\left((\hat{\theta}_{t_k} - \hat{\theta}_{t_1}, \ldots, \hat{\theta}_{t_k} - \hat{\theta}_{t_{k-1}})^t\right)\right\}^{-1}$
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  3. Calculate $\widetilde{\theta}_{t_k} = \hat{\theta}_{t_k} - \sum_{k'=1}^{k-1} \widehat{\lambda}_{k'}^{(k)} (\hat{\theta}_{t_k} - \hat{\theta}_{t_{k'}})$ and $\tilde{Z}_k = \frac{\tilde{\theta}_{t_k} - \theta_0}{\widehat{se}(\tilde{\theta}_{t_k})}$.

Theorem: Asymptotic Properties

Consider any sequence of RAL estimators $(\widehat{\theta}_{t_1}, \ldots, \widehat{\theta}_{t_K})$ with all components consistent for θ, and for which

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

and the covariance matrix $\boldsymbol{\Sigma}$ of the corresponding test statistics can be consistently estimated.

Then,

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

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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.

Outline

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)

Algorithm for Analysis Timing: Information

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

Algorithm for Analysis Timing: Information

- 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

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

(Mehta and Tsiatis, 2001; Zhang, 2009)

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, ...).

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  - Probability of success in control arm (binary endpoint), prognostic value of covariates, ...

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- Assessing feasibility by **estimating the number of participants** corresponding with the maximum information.
  - Usings 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.

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   - 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

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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  - Success rate: 25% in standard medical care group versus 38% in MISTIE group
- 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: $K = 2$

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

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 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 $\widetilde{\theta}_{t_k}$ 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**.