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

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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)

Problem Setting

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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**.
  - This can lead to unnecessary numbers of patients being exposed to an experimental treatment, which is **unethical**.

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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.

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  - e.g., *G-computation* estimator (as suggested in the recent FDA draft guidance on covariate adjustment)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
     - $\hat{E}(Y|A=1) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 + \hat{\gamma}_2 B_i)$
     - $\hat{E}(Y|A=0) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_2 B_i)$
  3. Calculate $\hat{\theta} = \hat{E}(Y|A=1) - \hat{E}(Y|A=0)$

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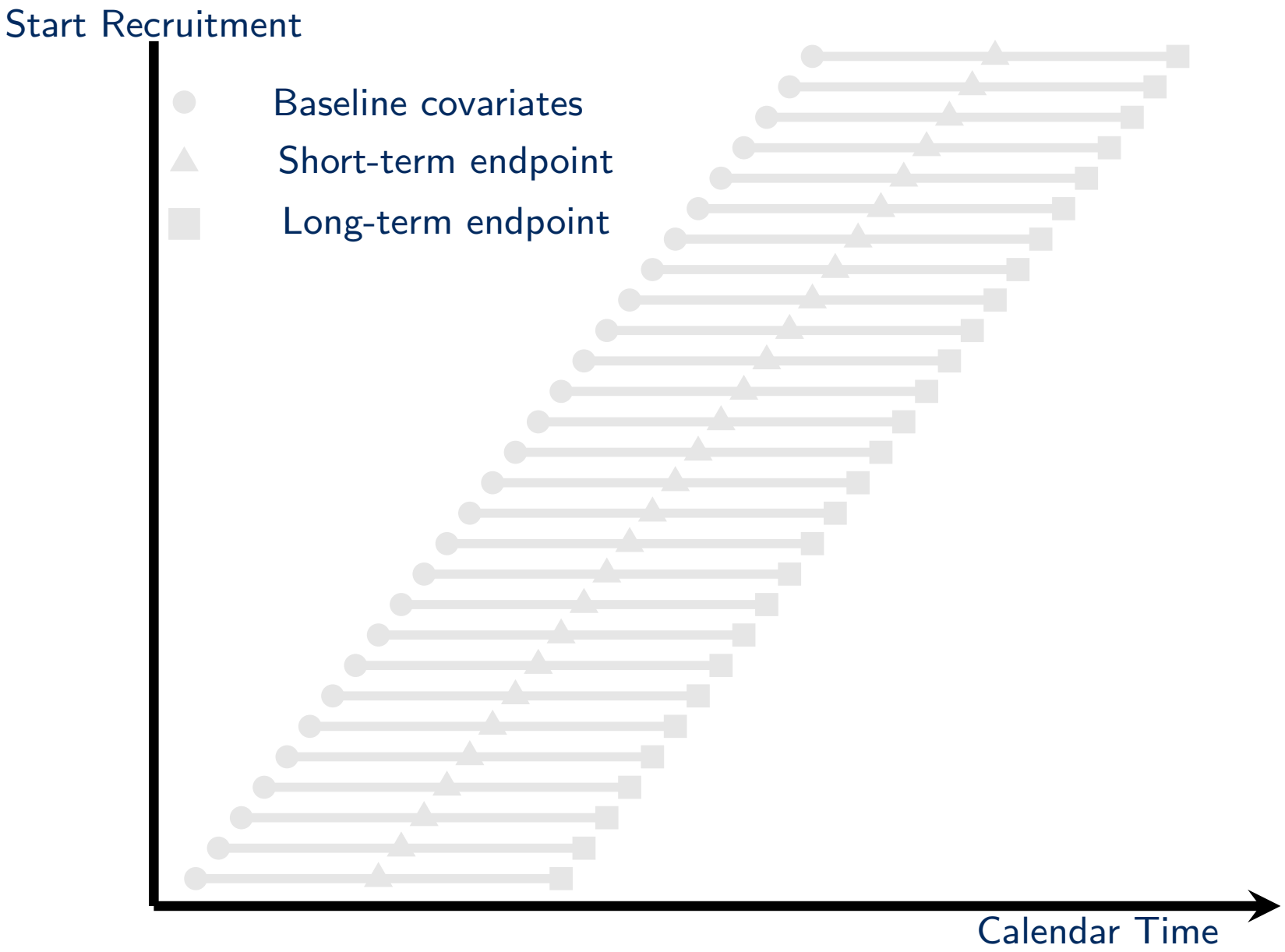
Group Sequential Design



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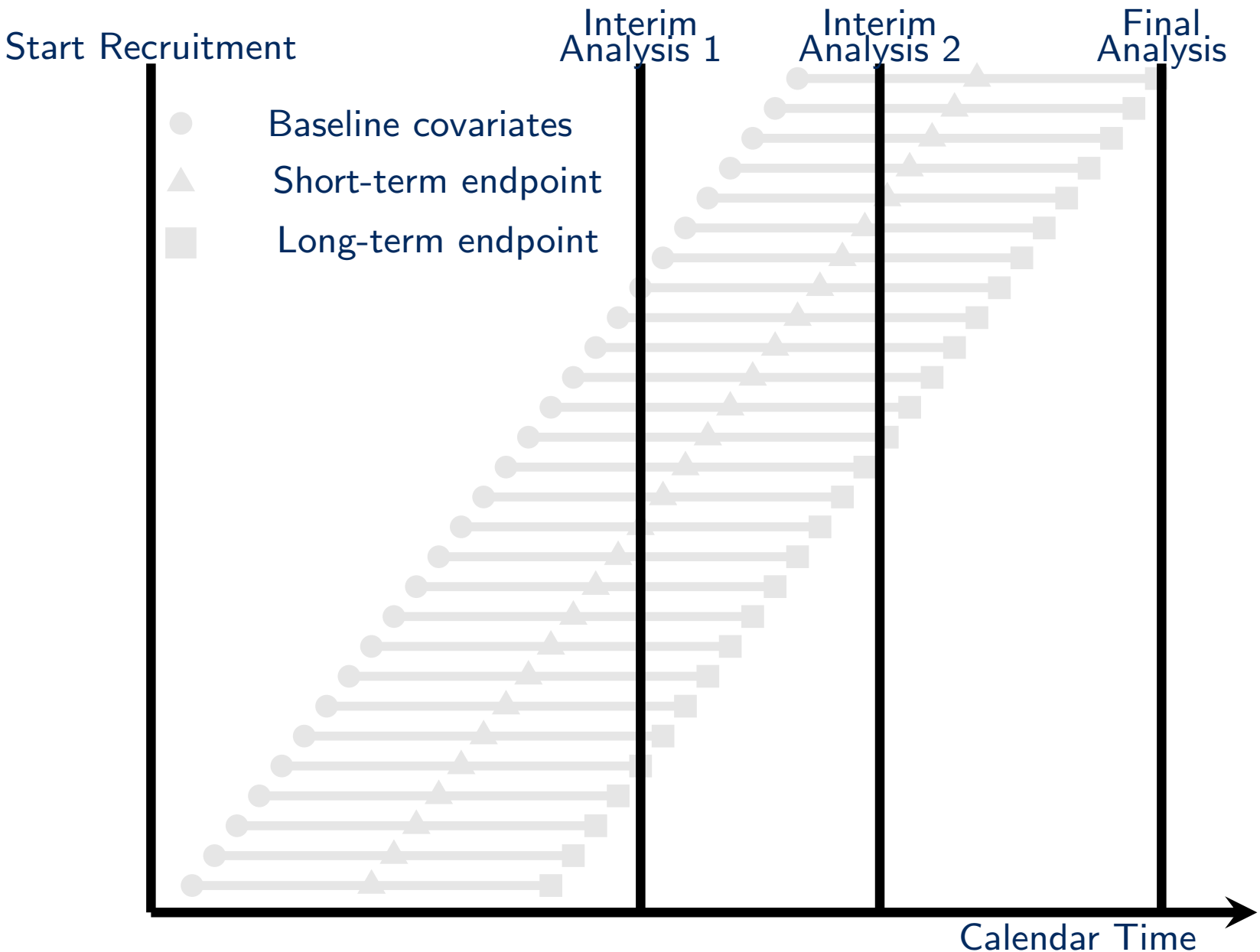

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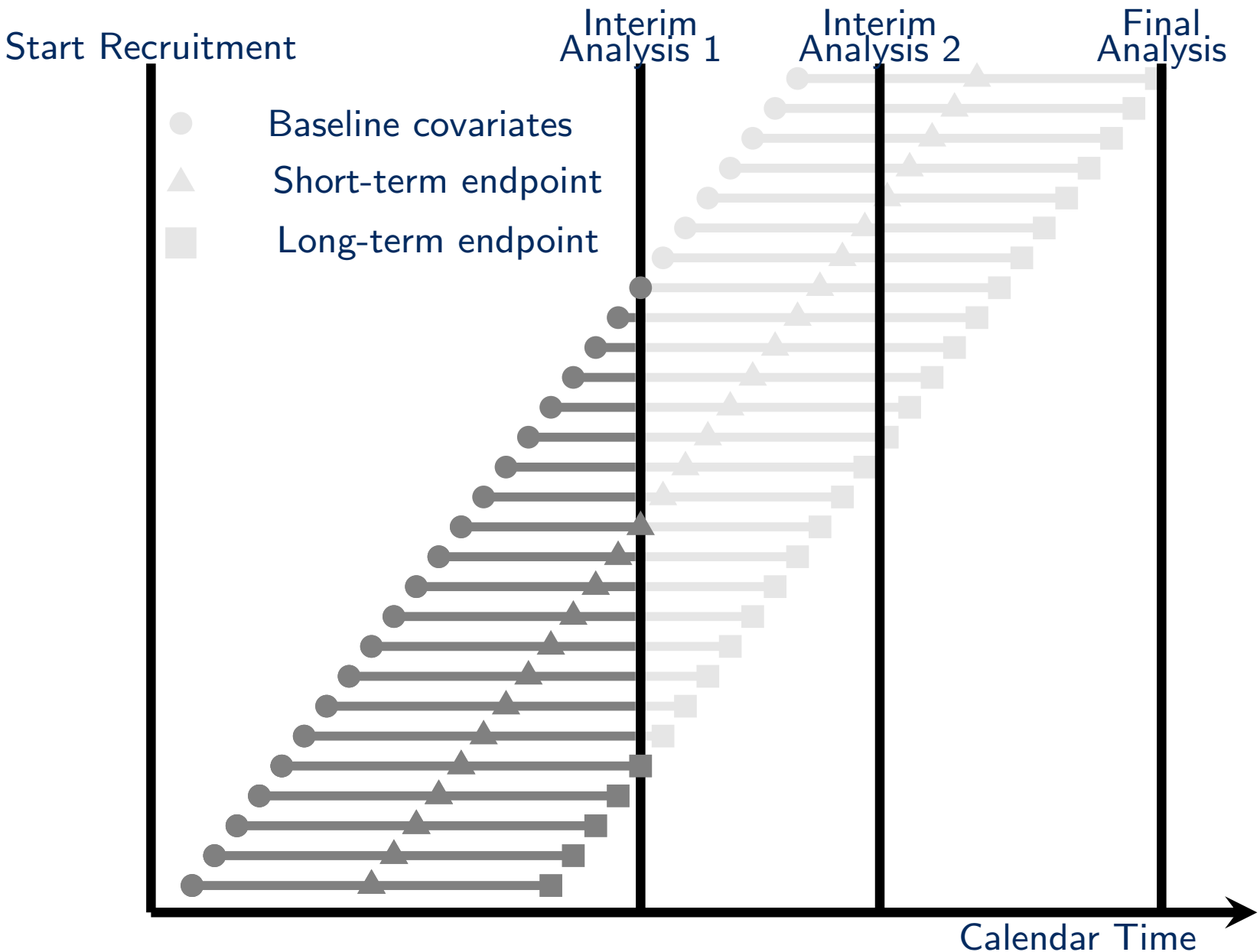

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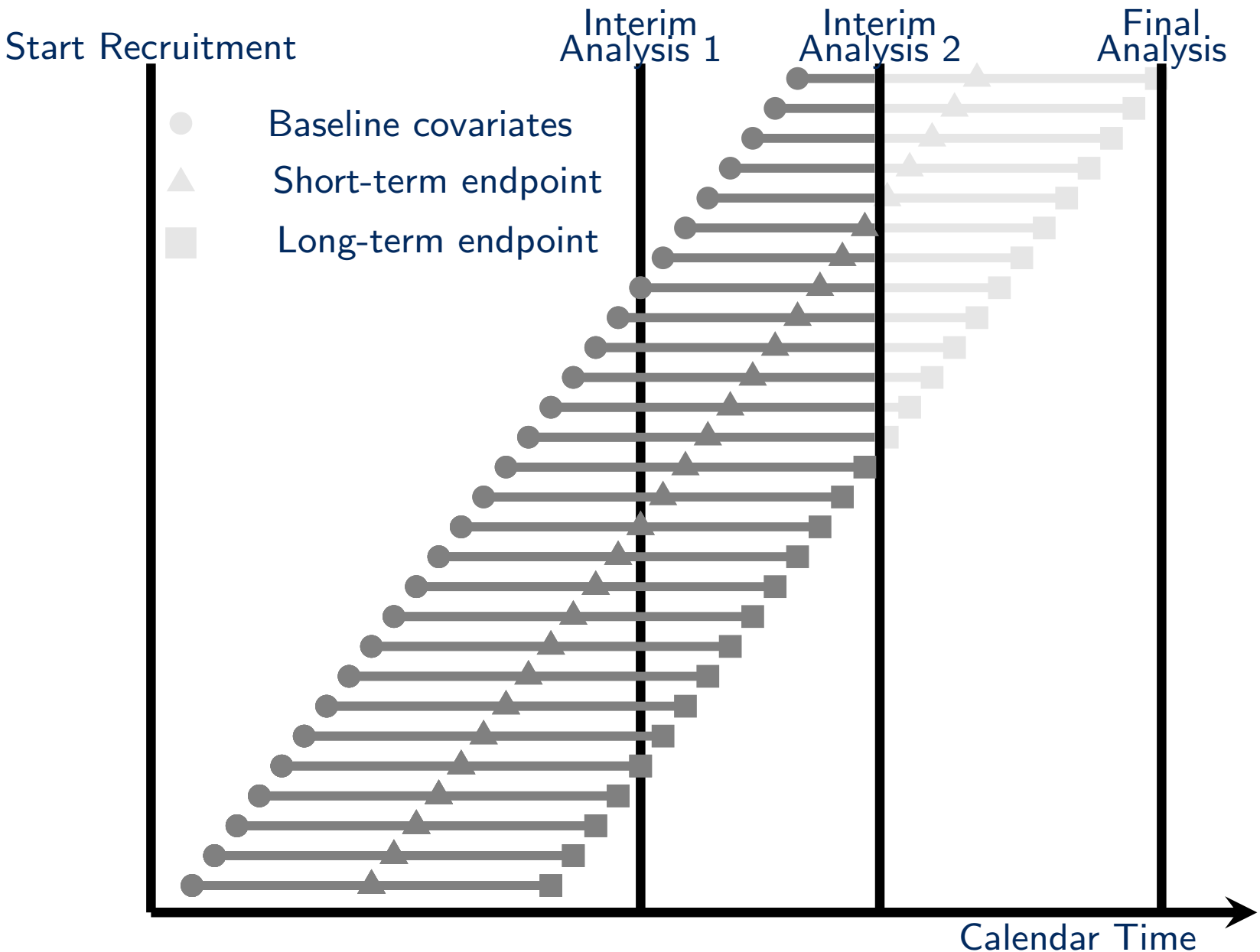

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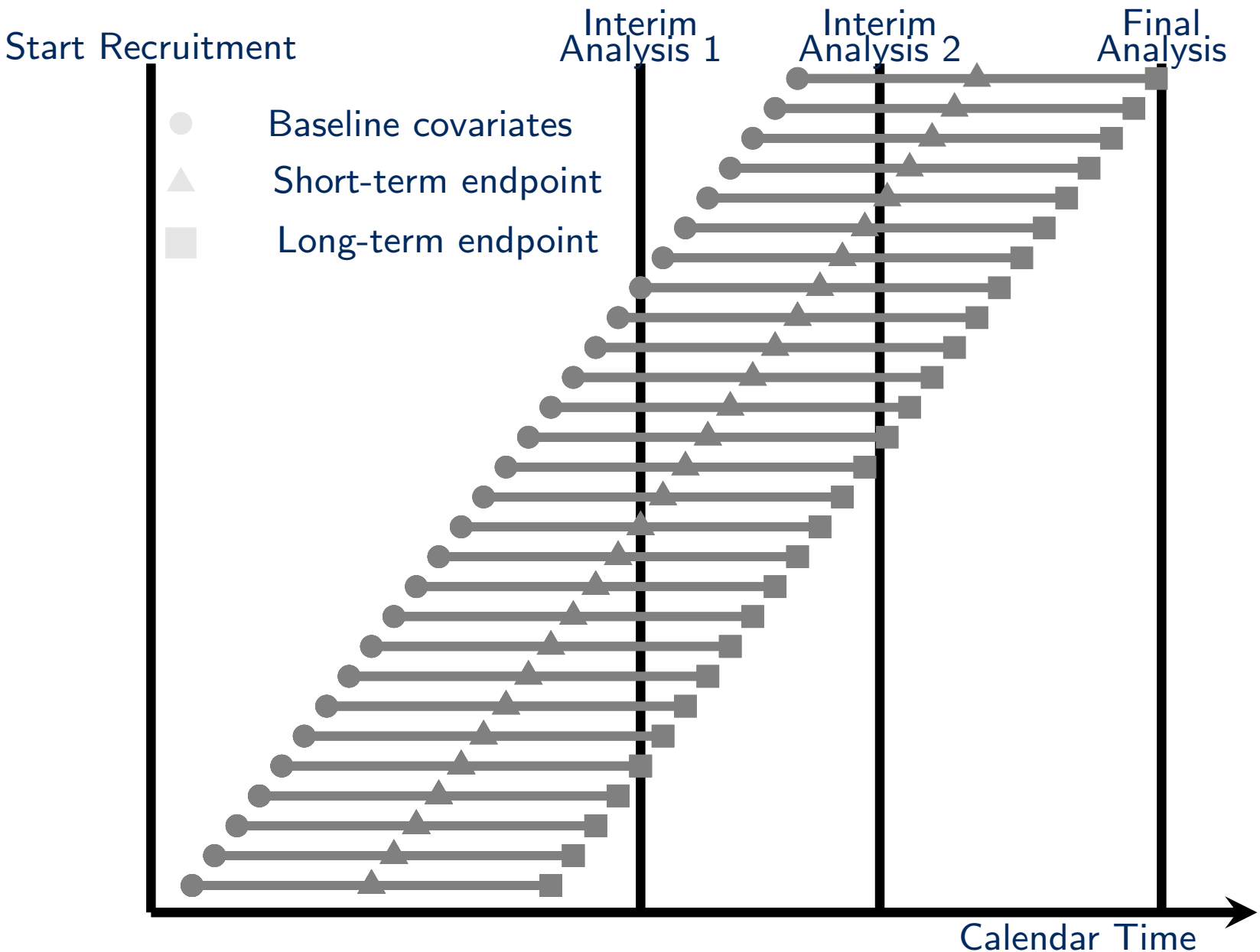

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Group Sequential Design

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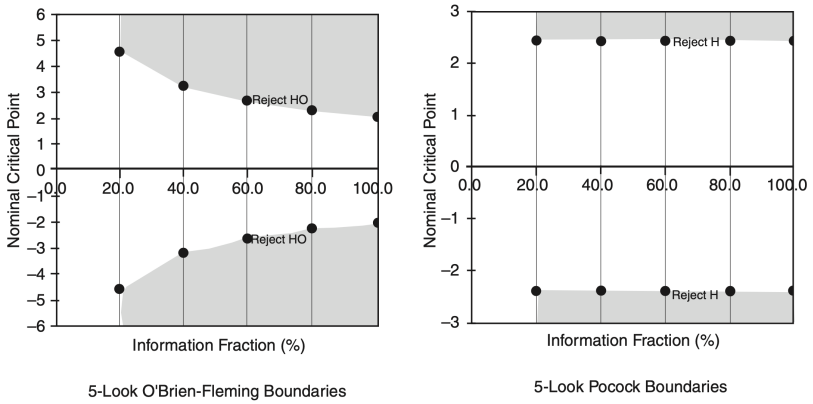
  - **Saving resources**
- Multiple looks at accumulating data **increase type I error**
  - Lower significant thresholds needs to be used for the interim analyses.
  - There are a range of methods for defining the critical values for interim analyses.

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

Group Sequential Designs: Popular Boundaries



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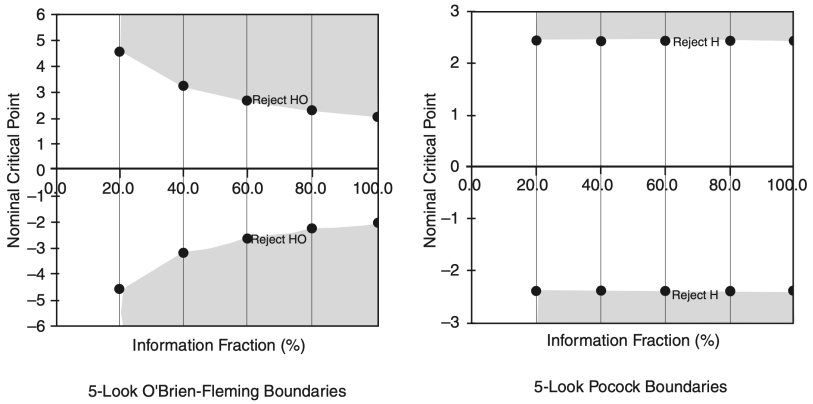

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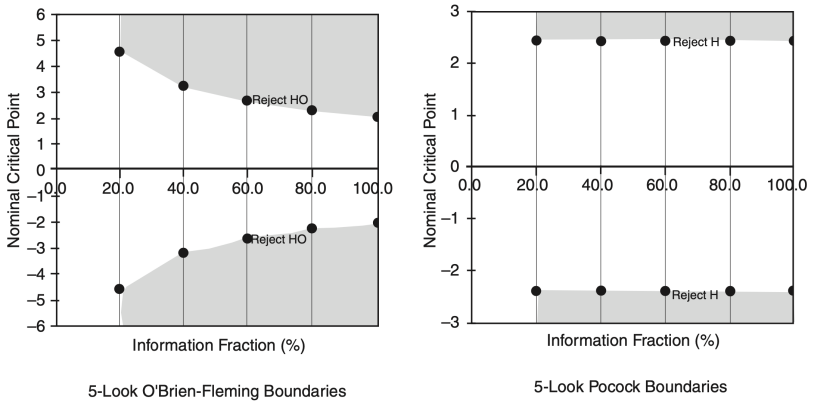

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  - Defined as the reciprocal of the (interim) estimator's variance.
  - This is estimated by $\hat{\mathcal{I}}_k = (\widehat{se}(\hat{\theta}_{t_k}))^{-2}$ for which we assume that $\lim_{n\to\infty} \hat{\mathcal{I}}_k/n = \lim_{n\to\infty} \left\{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

Independent Increments (1)

- Assume that

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

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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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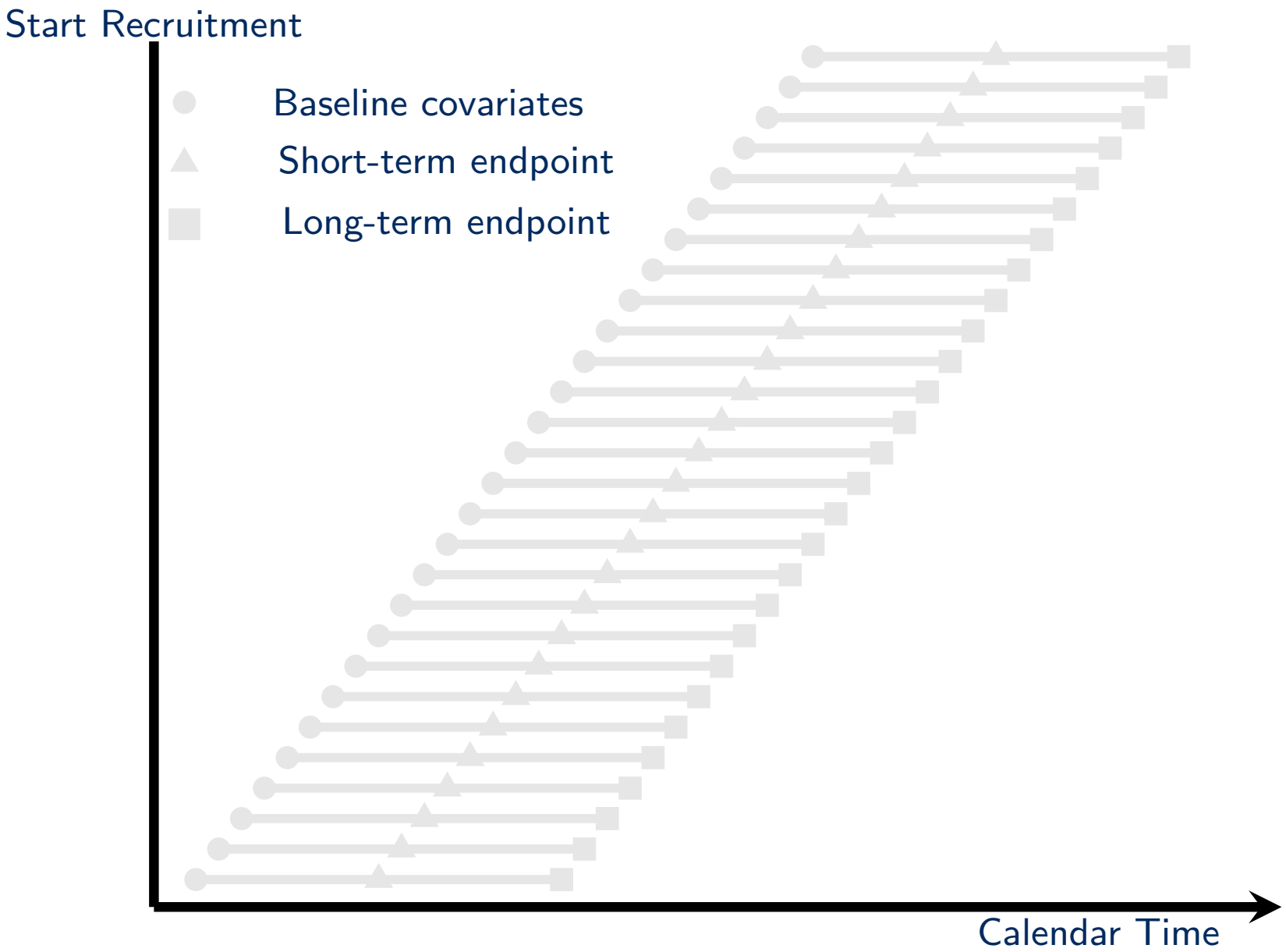

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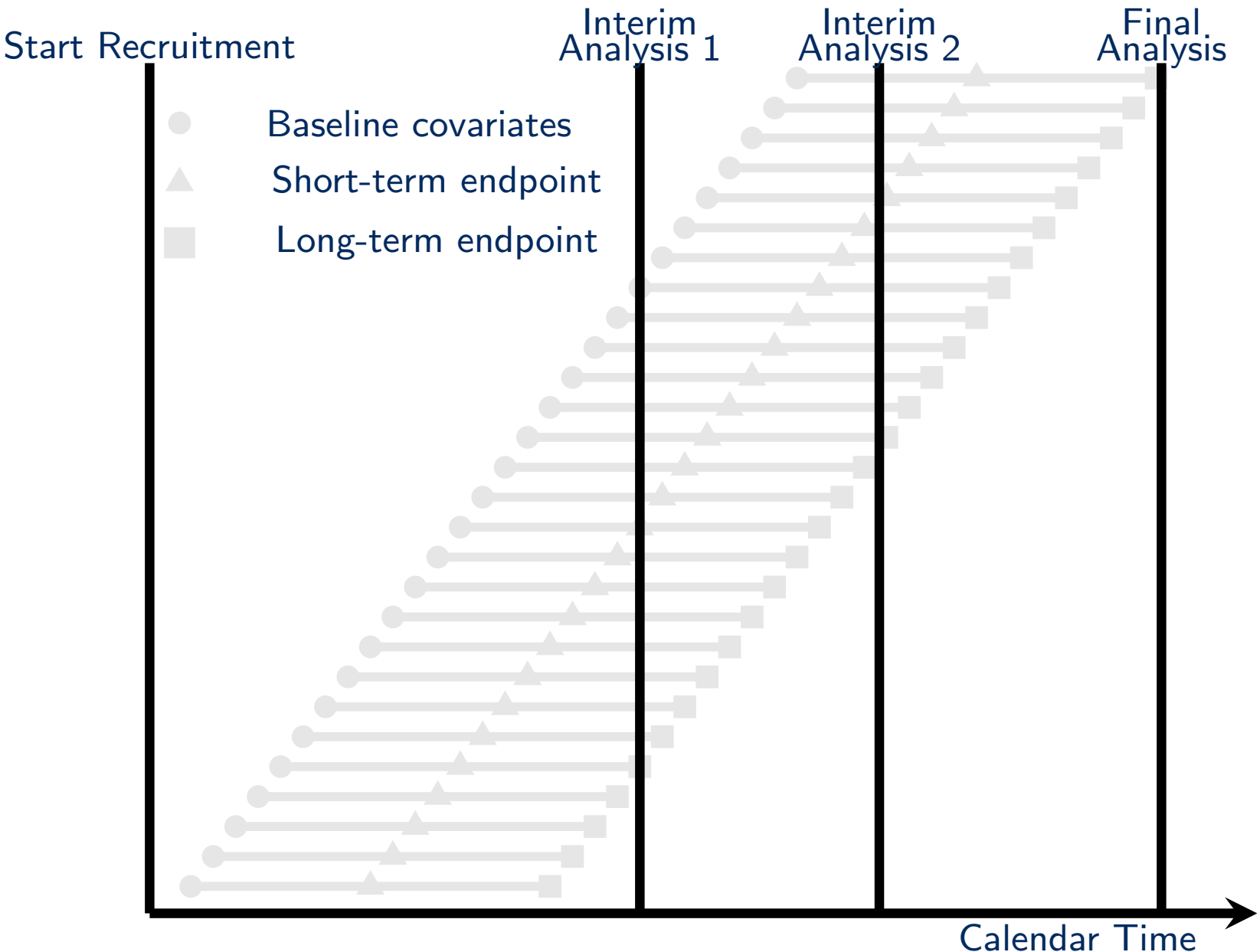

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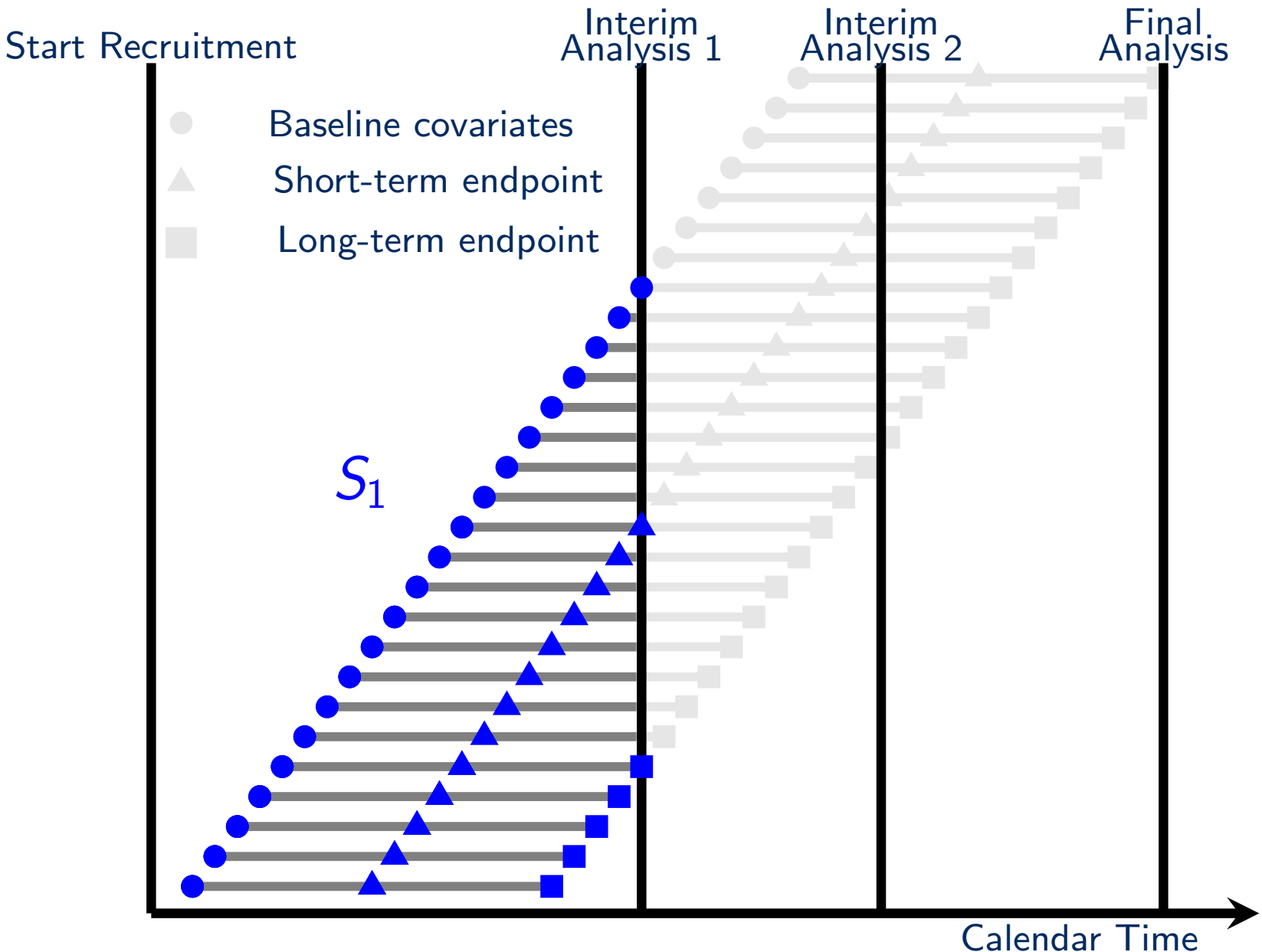

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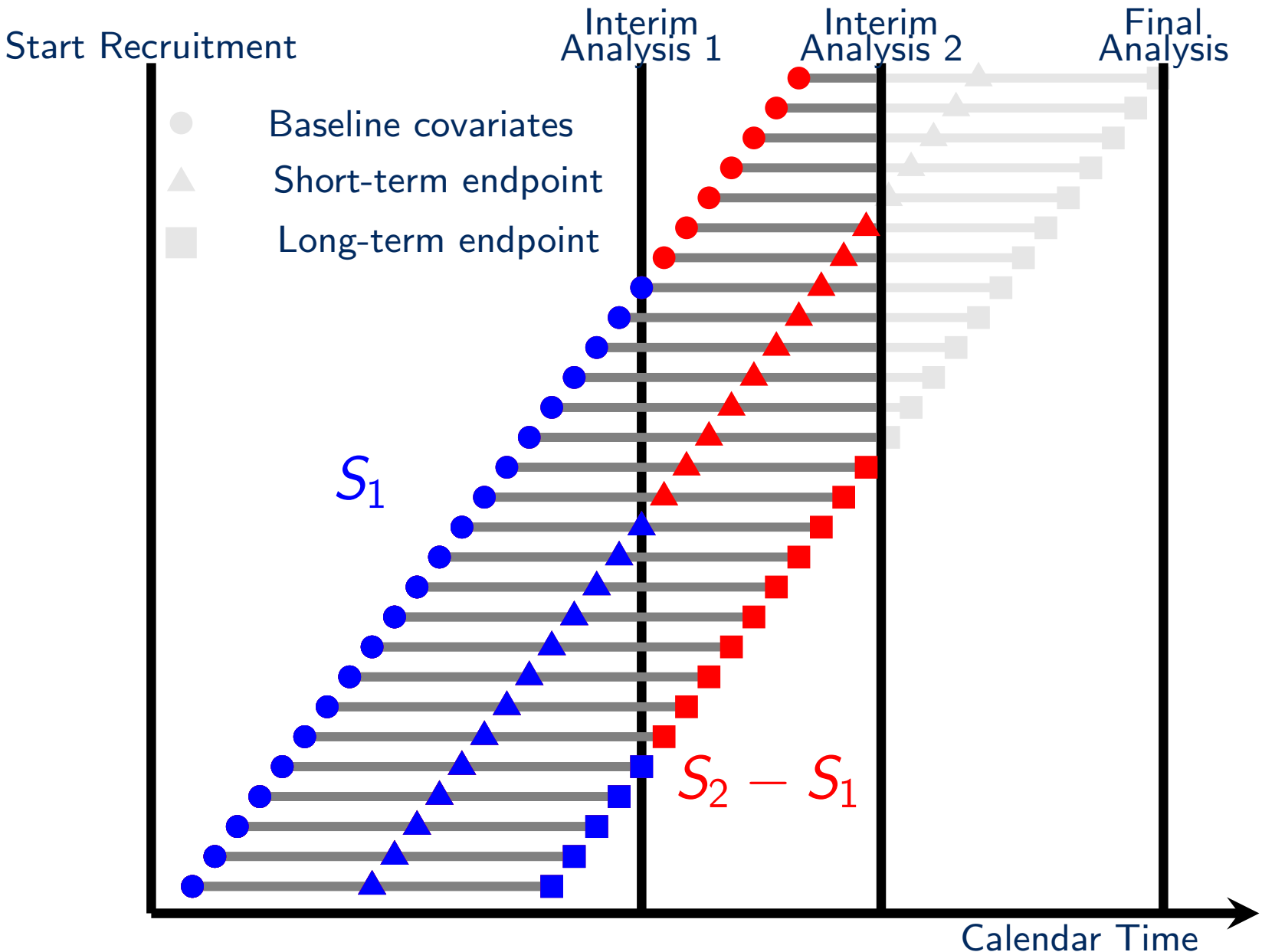

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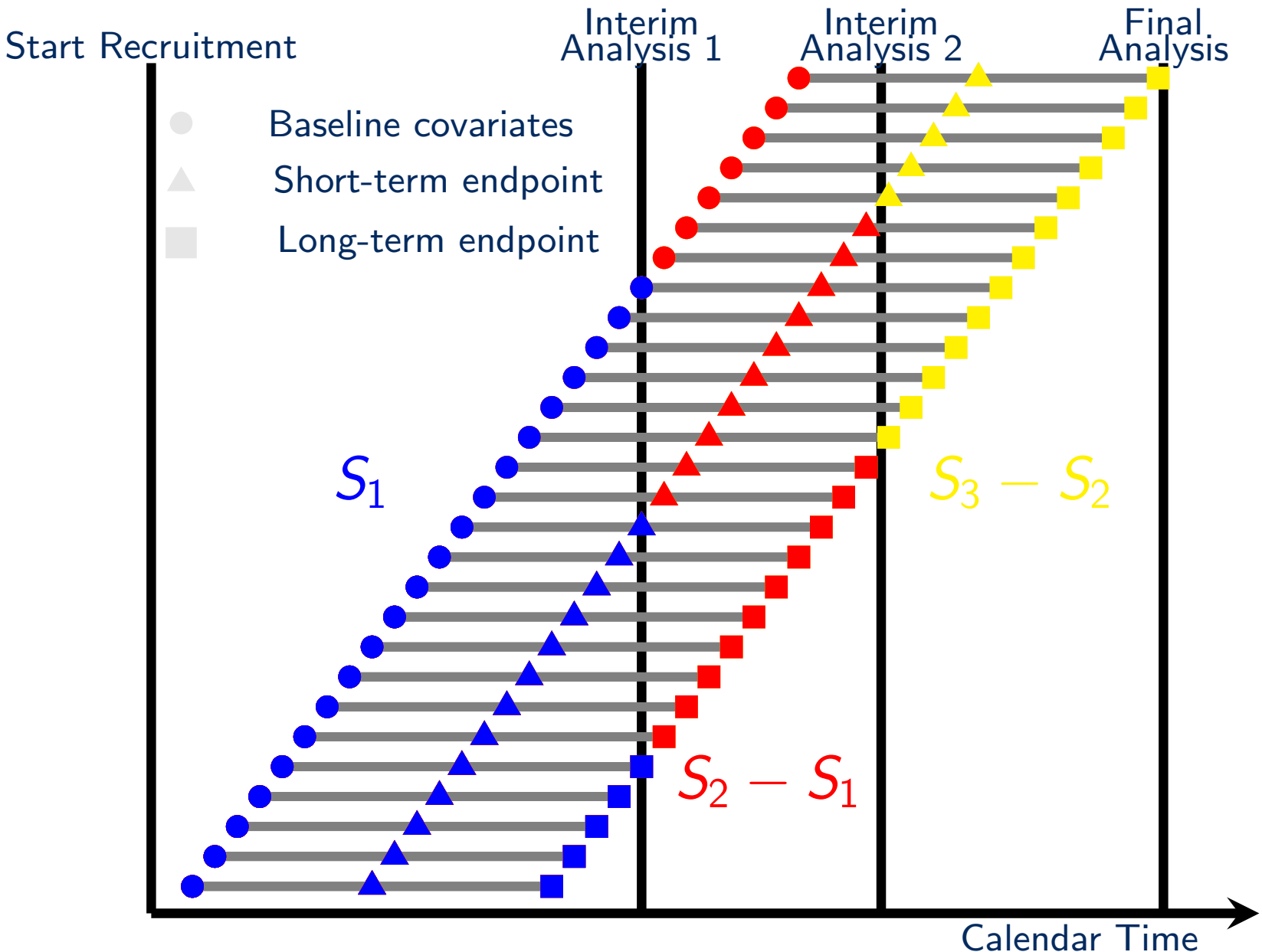

Independent Increments (4)

- On the estimator level, the general theory also implies that $\widehat{\theta}_{t_1}, \ldots \widehat{\theta}_{t_K}$ are asymptotically multivariate normal with
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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 $\widehat{\boldsymbol{\lambda}}^{(k)} = \left\{\widehat{Var}\left((\hat{\theta}_{t_k} - \hat{\theta}_{t_1}, \ldots, \hat{\theta}_{t_k} - \hat{\theta}_{t_{k-1}})^t\right)\right\}^{-1}$
$\cdot \widehat{Cov}\left(\hat{\theta}_{t_k}, (\hat{\theta}_{t_k} - \hat{\theta}_{t_1}, \ldots, \hat{\theta}_{t_k} - \hat{\theta}_{t_{k-1}})^t\right)$

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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

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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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- 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.

Obstacles Leading to Underutilization

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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: $K = 1$

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		$\theta = 0$ (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

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

References I

Benkeser, D., I. Díaz, A. Luedtke, J. Segal, D. Scharfstein, and M. Rosenblum (2020). Improving precision and power in randomized trials for covid-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes. *Biometrics*.

Jennison, C. and B. W. Turnbull (1997). Group-sequential analysis incorporating covariate information. *Journal of the American Statistical Association 92*(440), 1330–1341.

Jennison, C. and B. W. Turnbull (1999). *Group sequential methods with applications to clinical trials*. CRC Press.

Jiang, F., L. Tian, H. Fu, T. Hasegawa, and L. J. Wei (2018). Robust alternatives to ANCOVA for estimating the treatment effect via a randomized comparative study. *Journal of the American Statistical Association 0*, 1–37.

References II

Kim, K. and A. A. Tsiatis (2020). Independent increments in group sequential tests: a review. *SORT-Statistics and Operations Research Transactions*, 223–264.

Koch, G. G., C. M. Tangen, J.-W. Jung, and I. A. Amara (1998). Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. *Stat. Med. 17*(15-16), 1863–1892.

Lan, G. K. and D. L. DeMets (1983). Discrete sequential boundaries for clinical trials. *Biometrika 70*(3), 659–663.

Mehta, C. R. and A. A. Tsiatis (2001). Flexible sample size considerations using information-based interim monitoring. *Drug information journal: DIJ/Drug Information Association 35*(4), 1095–1112.

References III

Moore, K. and M. J. van der Laan (2009a). Covariate adjustment in randomized trials with binary outcomes: Targeted maximum likelihood estimation. *Stat. Med. 28*(1), 39–64.

Moore, K. L. and M. J. van der Laan (2009b). Increasing power in randomized trials with right censored outcomes through covariate adjustment. *Journal of Biopharmaceutical Statistics 19*(6), 1099–1131. PMID: 20183467.

O'Brien, P. C. and T. R. Fleming (1979). A multiple testing procedure for clinical trials. *Biometrics*, 549–556.

Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika 64*(2), 191–199.

References IV

Rosenblum, M., T. Qian, Y. Du, , and H. Qiu (2015). Adaptive enrichment designs for randomized trials with delayed endpoints, using locally efficient estimators to improve precision. *Johns Hopkins University, Dept. of Biostatistics Working Papers. https://biostats.bepress.com/jhubiostat/paper275*.

Rubin, D. and M. van der Laan (2008). Covariate adjustment for the intention-to-treat parameter with empirical efficiency maximization. *U.C. Berkeley Division of Biostatistics Working Paper Series. Working Paper 229*, https://biostats.bepress.com/ucbbiostat/paper229.

Scharfstein, D. O., A. A. Tsiatis, and J. M. Robins (1997). Semiparametric efficiency and its implication on the design and analysis of group-sequential studies. *J Am Stat Assoc 92*(440), 1342–1350.

References V

Shoben, A. B. and S. S. Emerson (2014). Violations of the independent increment assumption when using generalized estimating equation in longitudinal group sequential trials. *Statistics in medicine 33*(29), 5041–5056.

Tsiatis, A. A., M. Davidian, M. Zhang, and X. Lu (2008). Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. *Statistics in medicine 27*(23), 4658–4677.

Yang, L. and A. Tsiatis (2001). Efficiency study of estimators for a treatment effect in a pretest-posttest trial. *The American Statistician 55*(4), 314–321.

Zhang, D. (2009). Lecture notes for statistical principles of clinical trials (modified from dr. a. tsiatis' lecture notes).

References VI

Zhang, M. (2015, Jan). Robust methods to improve efficiency and reduce bias in estimating survival curves in randomized clinical trials. *Lifetime Data Analysis 21*(1), 119–137.

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**.