Improving interim decisions for single-arm trials by adjusting for baseline covariates and short-term endpoints

Eline Anslot

Joint work with Kelly Van Lancker

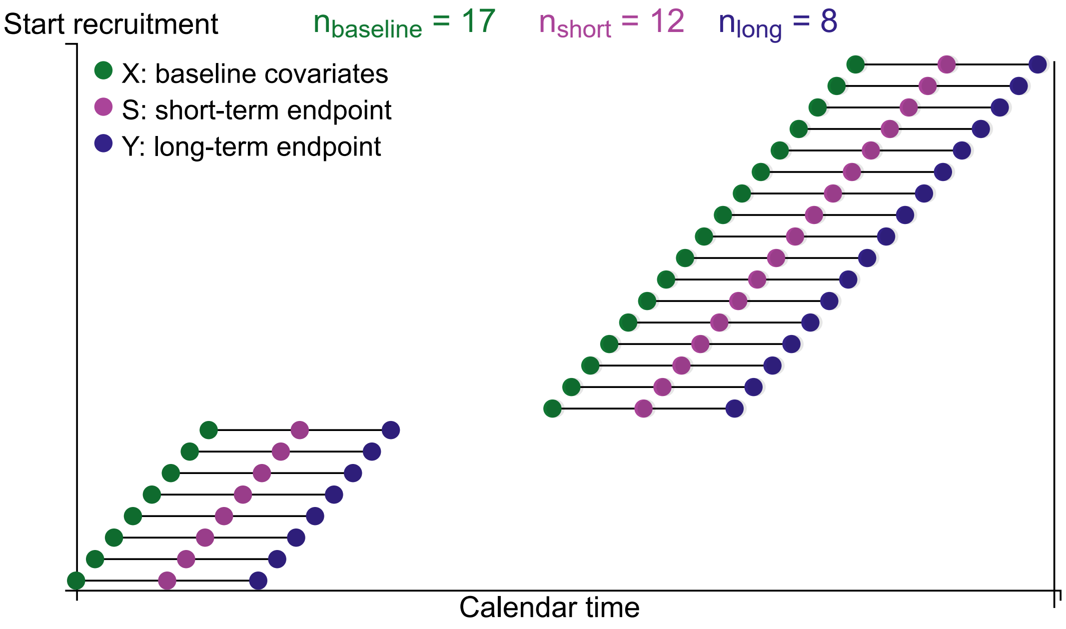
GHENT UNIVERSITY

Table of content

1. **Single-arm trials combined with multi-stage designs**
2. Proposed method
3. Simulations
4. Discussion

GHENT UNIVERSITY

Single-arm trials with multi-stage designs

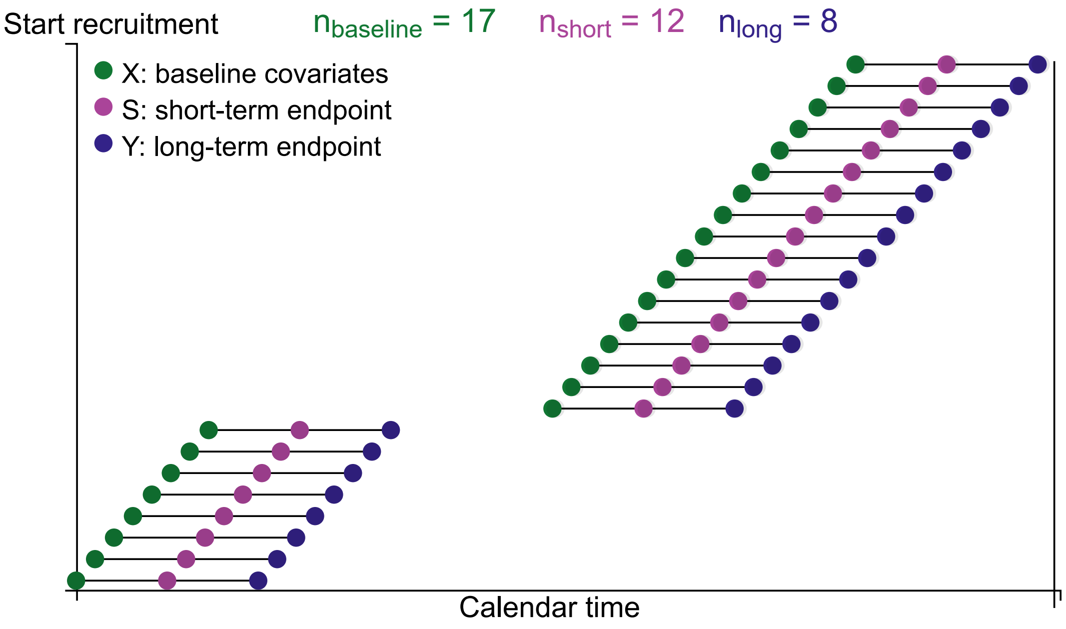


Commonly used designs:

- Group sequential designs
- Simon's two-stage designs

Continued/Paused

Interim analysis of two-stage designs



Continued/Paused

Interim analysis: based on the long-term endpoint ⇒ Unadjusted analysis

- **Simon's two-stage design:**

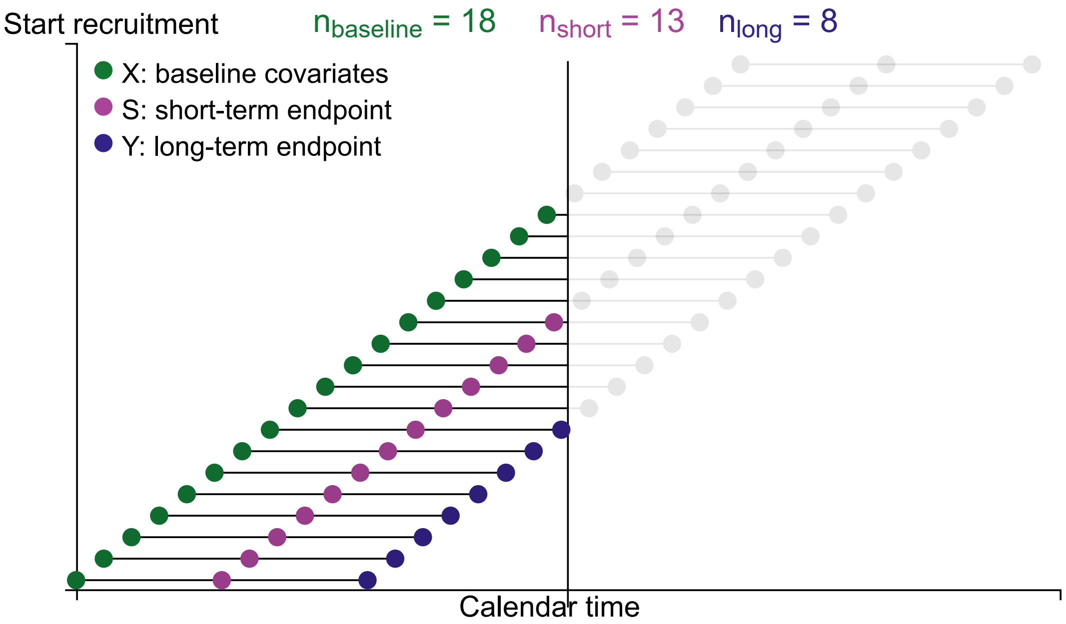
$$\sum_{i=1}^{n_{long}} y_i \leq r_1$$

- **Group sequential designs:**

$$Z = \frac{\frac{1}{n_{long}} \sum_{i=1}^{n_{long}} y_i - p_0}{SE\left(\frac{1}{n_{long}} \sum_{i=1}^{n_{long}} y_i\right)}$$

with Z compared to cut-off to stop a trial for futility or efficacy based on e.g., Pocock (1977), O'Brien and Fleming (1979) or Lan and DeMets (1983) $\alpha-$ or $\beta-$ error spending functions

Can we use more information?

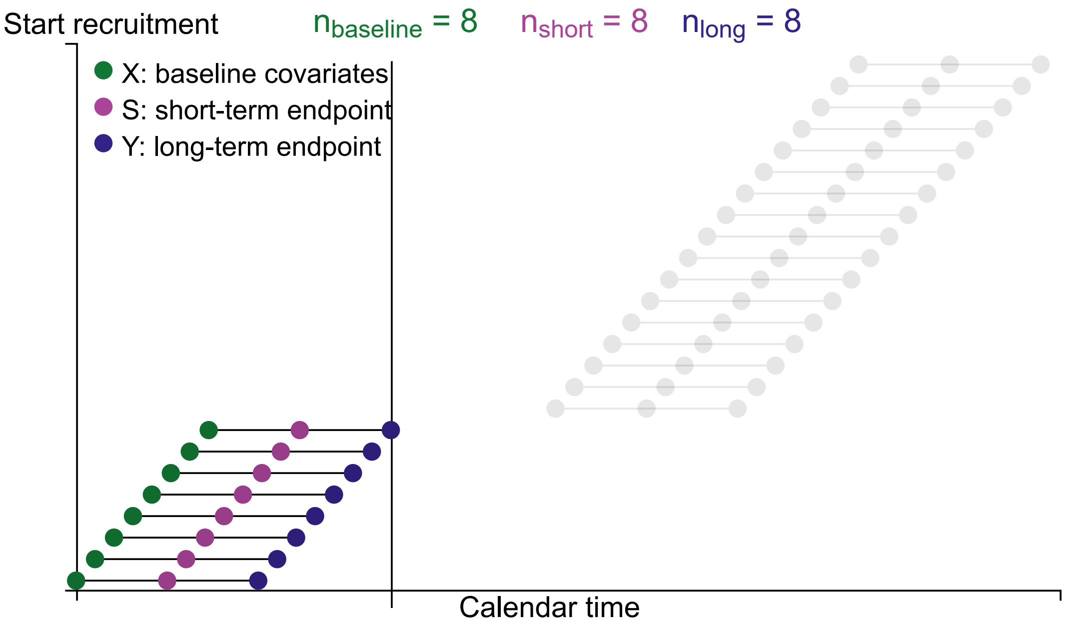


Unadjusted analysis

Reset

Adjusted analysis

Improve decision by short-term endpoint



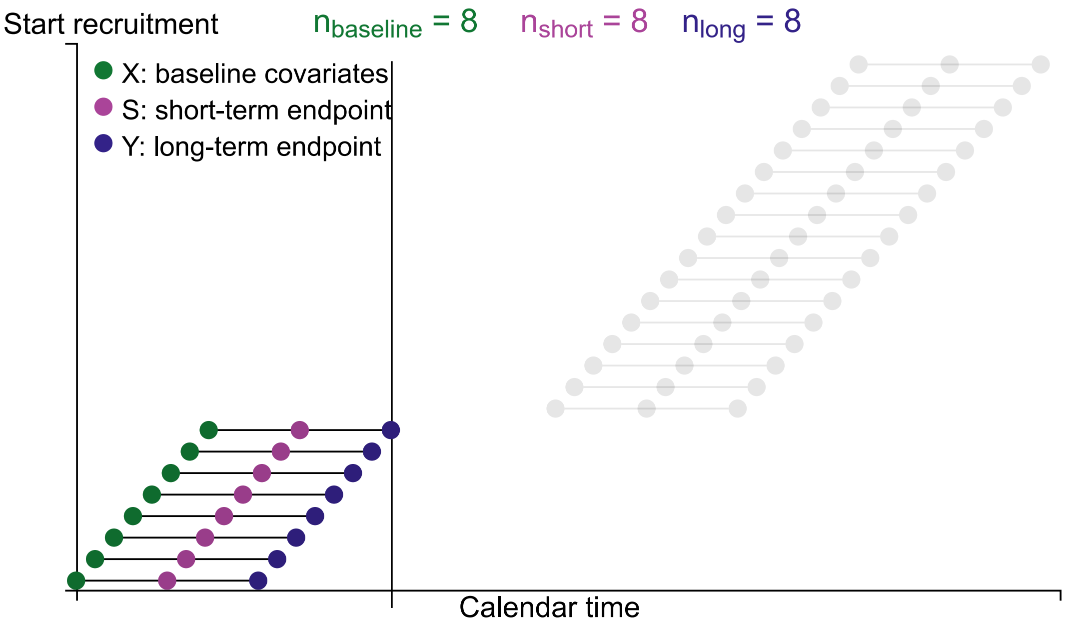
Unadjusted analysis

Kunz et al. (2017)

Zocholl et al. (2023)

Reset

More precise interim estimator



Continued/Paused

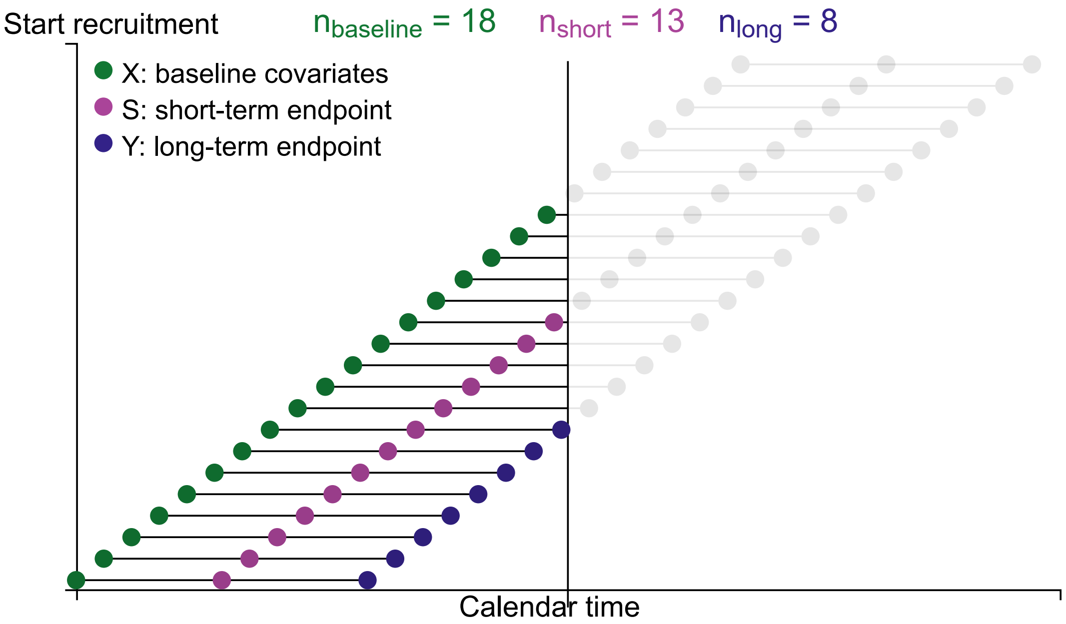
- **Recruitment with a pause:** Possible as in Kunz et al. (2017) and Zocholl et al. (2023)
- **Continuous recruitment**: ⇒ Focus of the talk

Table of content

1. Single-arm trials combined with multi-stage designs
2. **Proposed method**
3. Simulations
4. Discussion

GHENT UNIVERSITY

Proposed method



Step 1: Model fitting in cohort 1:

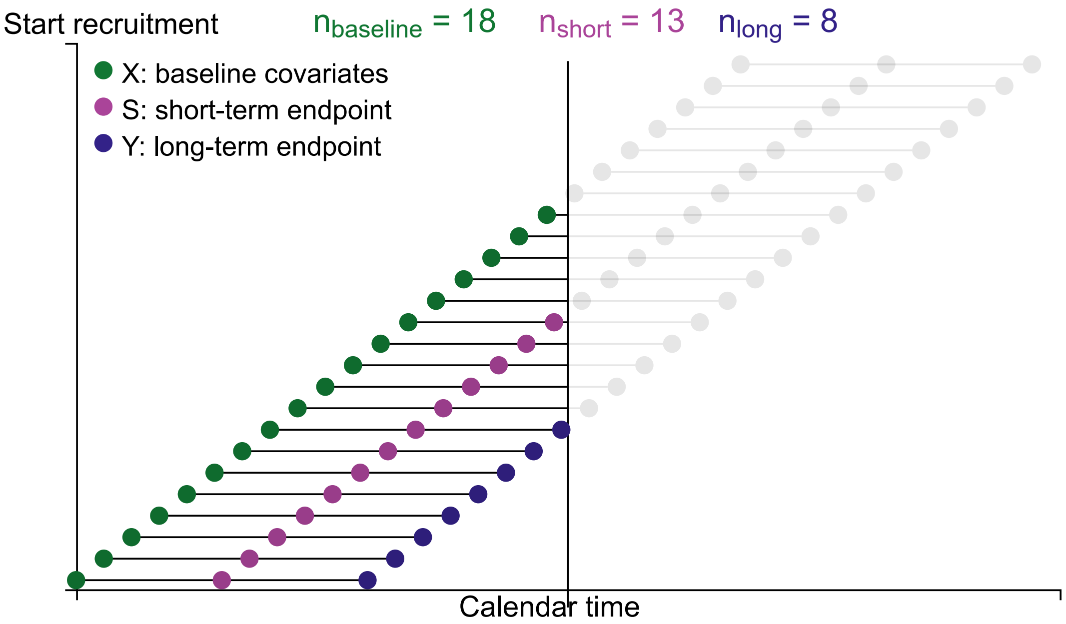
$$h[E(Y \mid X, S)] = \beta_0 + \boldsymbol{\beta}_1 X + \beta_2 S$$

h(.): canonical link function

Step 2: Predicting in cohort 1 and 2:

$$\hat{Y} = h^{-1}[\hat{\beta}_0 + \hat{\boldsymbol{\beta}}_1 X + \hat{\beta}_2 S]$$

Proposed method



Step 3: Model fitting in cohort 1 and 2:

$$h[E(\hat{Y} \mid X)] = \gamma_0 + \boldsymbol{\gamma}_1 X$$

Step 4: Predicting in cohort 1, 2 and 3:

$$\hat{Y}' = h^{-1}[\hat{\gamma}_0 + \hat{\boldsymbol{\gamma}}_1 X]$$

Step 5: Averaging

$$\hat{p}_{int} = \frac{1}{n_{baseline}} \sum_{i=1}^{n_{baseline}} \hat{Y}_i'$$

Proposed method - Decision at interim

Decision at interim:

$$Z_{int} = \frac{\hat{p}_{int} - p_0}{SE(\hat{p}_{int})}$$

In Group Sequential Design:

Z_{int} compared to cut-off to stop a trial for futility or efficacy based on e.g.,

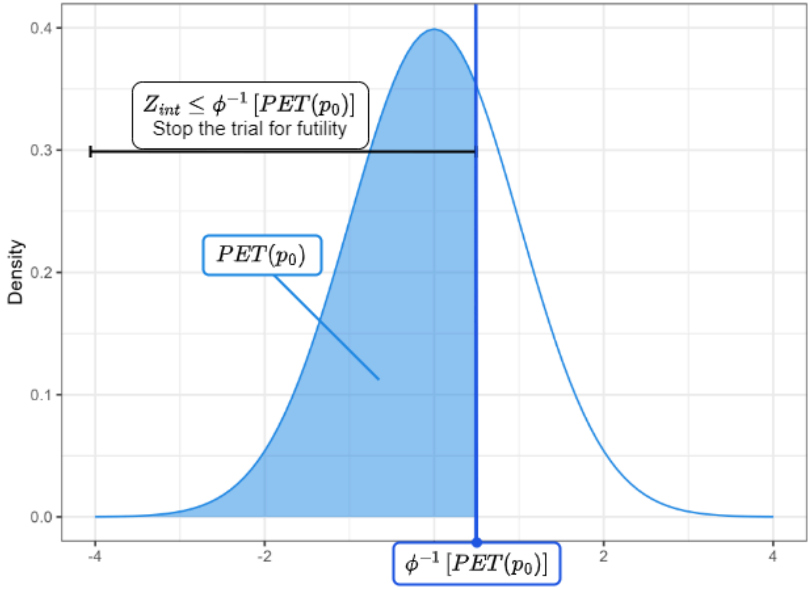
Pocock (1977), O'Brien and Fleming (1979) or

Lan and DeMets (1983) $\alpha-$ or $\beta-$ error spending functions

In Simon's Two-Stage:

$$Z_{int} \leq \phi^{-1}[PET(p_0)]$$

with $PET(p_0) = B(r_1; n_{long}, p_0)$



Proposed method

Decision at interim:

- Adjusting for multiple short-term endpoints and baseline covariates
- Asymptotically unbiased even with misspecified models
    - Under random recruitment
- Asymptotically efficient when models are correct

Table of content

1. Single-arm trials combined with multi-stage designs
2. Proposed method
3. **Simulations**
4. Discussion

GHENT UNIVERSITY

Simulation settings

$\alpha = 0.05$, power $= 0.80$

Design: two different optimal two-stage designs to generate e.g., n_{long} and r_1

Design	p_0	p_A	n_{final}	n_{long}	r_1	PET(p_0)
1	.25	.35	**149**	**56**	15	**.6853**
2	.25	.30	**522**	**223**	57	**.6112**

Setting 1:

Design	Adjustment		$n_{interim}$		Proportion n_{short}	Degree of Predictivity
	Baseline covariate(s)	Short-term endpoint	n_{long}	n_{short}		
1	/	1	56	15	0.20	Low to High
				25	0.30	
				58	0.50	
				86	0.60	
2	/	1	223	58	0.20	Low to High
				99	0.30	
				228	0.50	
				299	0.60	

Simulation settings

$\alpha = 0.05$, power $= 0.80$

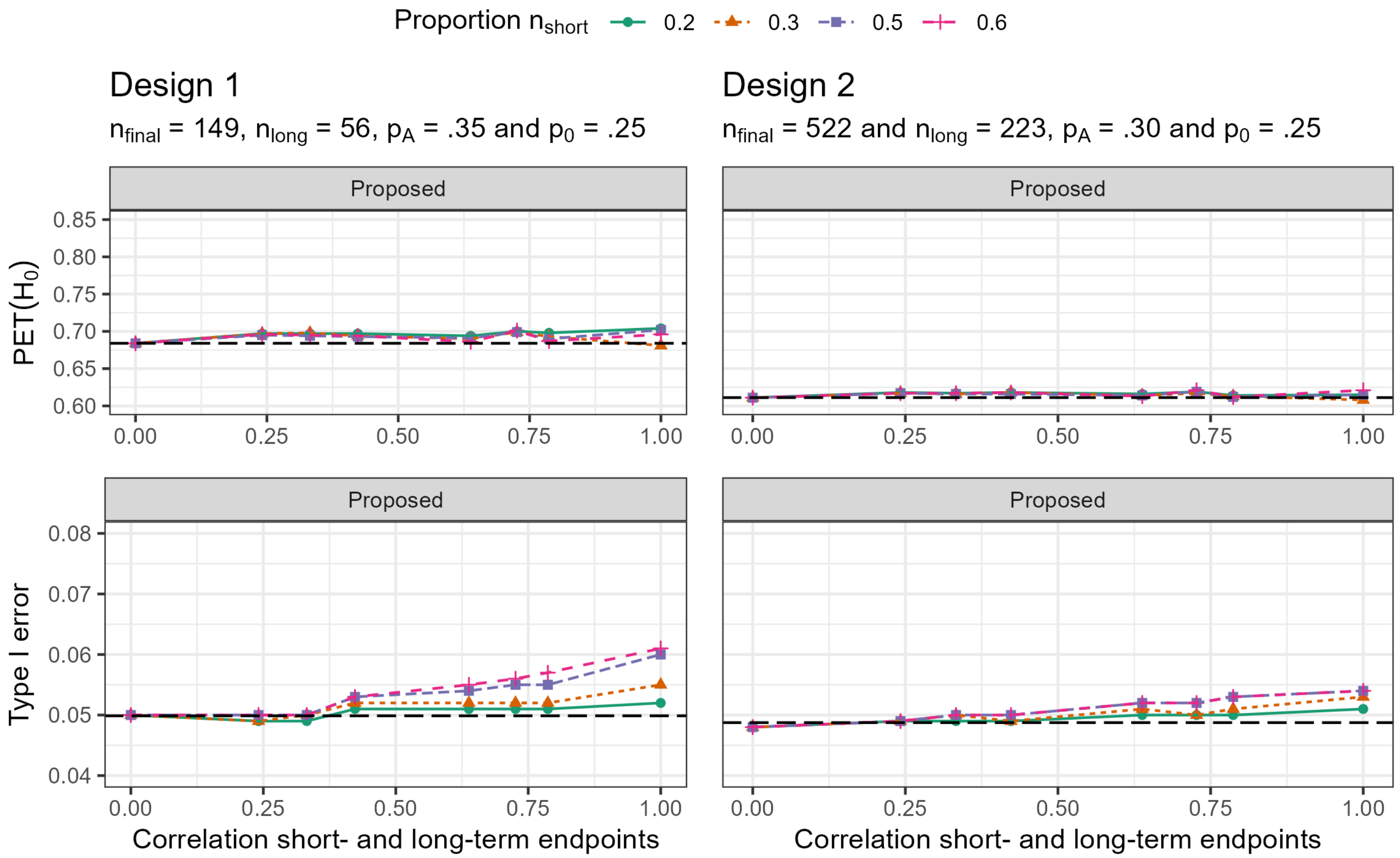
Design: two different optimal two-stage designs to generate e.g., n_{long} and r_1

Design	p_0	p_A	n_{final}	n_{long}	r_1	$PET(p_0)$
1	.25	.35	**149**	**56**	15	**.6853**

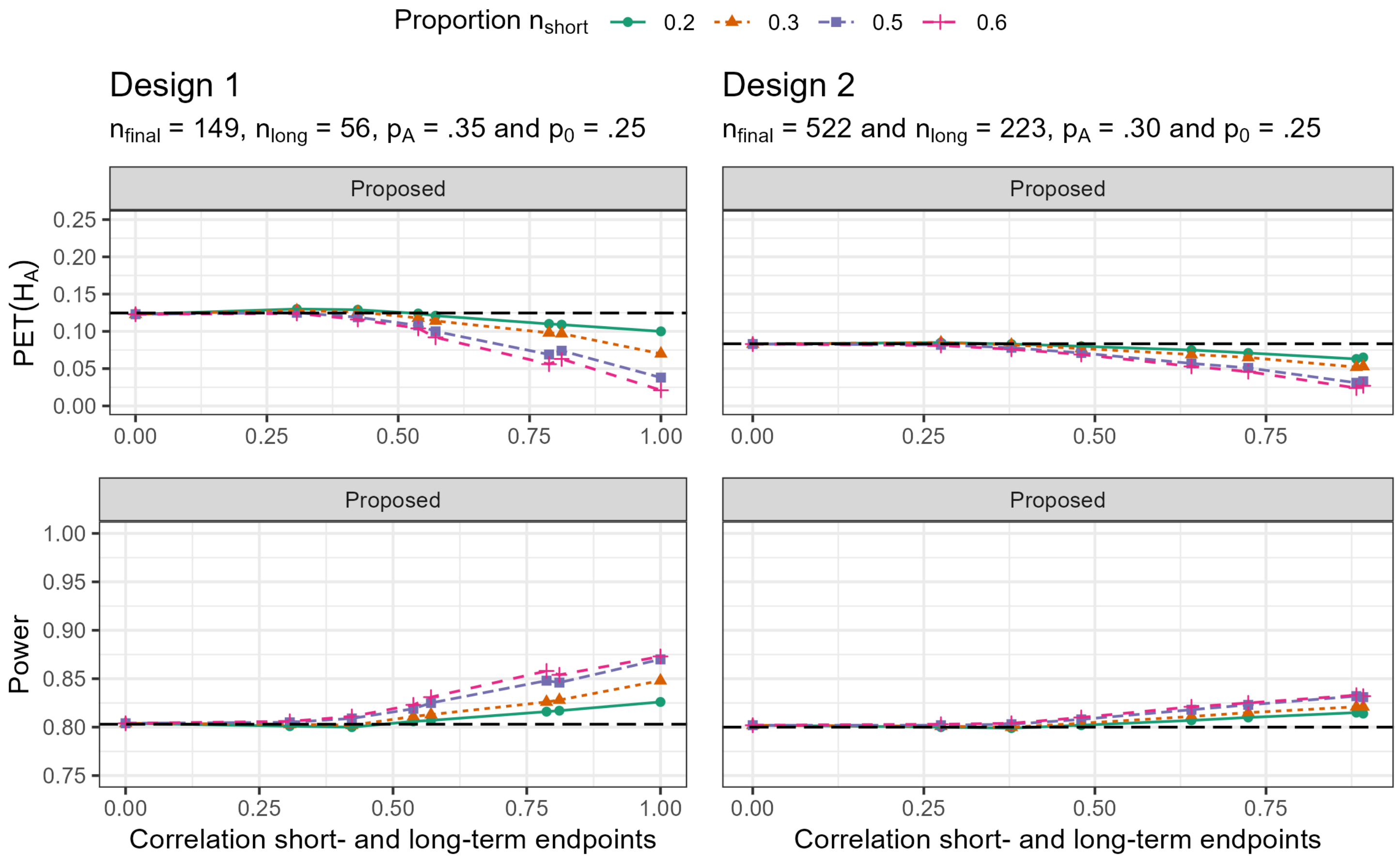
Setting 2:

Design	Adjustment		$n_{interim}$			Degree of Predictivity	Models	
	Baseline covariate(s)	Short-term endpoint	$n_{cohort1}$	$n_{cohort2}$	$n_{cohort3}$		Correct	Misspecified
1	3	1	56	29	29	Low, Moderate, High	✓	✗

Setting 1 - Under the null hypothesis



Setting 1 - Under the alternative hypothesis



Setting 2 - Model mispecification

Models	**Degree of predictivity**	**power**
Correct	Not predictive	79.7%
	Moderately predictive	82.4%
	Highly predictive	84.6%
Main	Not predictive	79.6%
	Moderately predictive	82.4%
	Highly predictive	84.7%
$\|X_1\|$	Not predictive	79.9%
	Moderately predictive	80.2%
	Highly predictive	80.8%

Table of content

1. Single-arm trials combined with multi-stage designs
2. Proposed method
3. Simulations
4. **Discussion**

GHENT UNIVERSITY

Discussion

Additional gain of the proposed method, depends on:

- Proportion of additional participants in the pipeline
  - But ideally not everybody should be recruited at interim
- Predictivity of baseline covariates and short-term endpoint
- Model misspecification
  - Extension: data-adaptive methods to help build the models (see e.g., Van Lancker et al., 2024)

Discussion

- Calculate sample size as if no power gain occured
- Type I error rate inflated in small sample
    - Estimator's variance leans on asymptotic theory
    - Decision at interim relies on approximation of standard normal distribution
        - Alternatives: exact logistic regression, Firth correction, and Bayesian logistic regression

Thank you for your attention

Questions?

GHENT UNIVERSITY