UniversitätsKlinikum Heidelberg

Blinded sample size re-calculation in clinical trials with binary composite endpoints based on correlation-adjusted local significance levels

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Outline

- Motivation
- Scenario
  - Analysis strategy
  - Sample size calculation / assumptions
- Internal pilot study design (IPS)
- Type I error
- Power
- Summary and outlook

Motivation – clinical trial example

Indication: Angina or acute coronary syndrome
Control (C): Bare metal stents
Intervention (I): Drug-eluting stents

Two primary binary endpoints:

- MACE at 9 months
- Cardiac death at 9 months

Composite endpoint (CE)

Main component (MC)

Analysis: Significant result in at least one of both endpoints required

MACE: Major adverse cardiac event (cardiac death, MI (myocardial infarction), ischaemia-driven TVR (target vessel revascularization))

Analysis

$X^C = (X^C_{MC}, X^C_{other}),\ X^C \sim Multinom(n, p^C_{MC}, p^C_{other})$
$X^I = (X^I_{MC}, X^I_{other}),\ X^I \sim Multinom(n, p^I_{MC}, p^I_{other})$

Chi²-test statistics: $\chi^2_{CE},\ \chi^2_{MC}$

$$\chi^2 = \frac{n\,(x^C(n^I - x^I) - x^I(n^C - x^C))^2}{n^C n^I x(n-x)}, \quad \text{with} \quad \begin{matrix} n = n^C + n^I \\ x = x^C + x^I \end{matrix}$$

Bonferroni adjustment to account for multiple testing

→ $\alpha_{CE} = \alpha_{MC} = 0.0125$ (one-sided)

Correlation of endpoints and test statistics lead to conservative test decisions → increase of local significance levels?

Alpha adjustment (Rauch and Kieser 2012)

$$X^C = (X^C_{MC}, X^C_{other}),\ X^C \sim Multi(n, p^C_{MC}, p^C_{CE-MC})$$
$$X^I = (X^I_{MC}, X^I_{other}),\ X^I \sim Multi(n, p^I_{MC}, p^I_{CE-MC})$$

Correlation of the test statistics (under H_0) is given by

$$Corr(\chi^2_{CE}, \chi^2_{MC}) \approx Corr(X^C_{CE}, X^C_{MC})$$

$$Corr(X^C_{CE}, X^C_{MC}) = \frac{p^C_{MC}\,(1-p^C_{CE})}{\sqrt{p^C_{CE}\,(1-p^C_{CE})\,p^C_{MC}(1-p^C_{MC})}}$$

$$\alpha = 1 - \theta\,(z_{1-\alpha_{CE}}, z_{1-\alpha_{MC}})$$

- flexible alpha splitting
- in the following given to α_{CE}

Clinical trial example (continued)

Two primary binary endpoints:

- MACE at 9 months
- Cardiac death at 9 months

Analysis: Significant result in at least one of both endpoints required

- Chi²-test
- Bonferroni adjustment (multiple testing)
- Alpha adjustment (using correlation of test statistics; according to Rauch and Kieser 2012)

Planning: Sample size calculation

Sample size calculation

Ingredients:

- Overall event rates (p_{CE}, p_{MC}) and effect sizes (Δ_{CE}, Δ_{MC})
- Global (α=0.025) and local significance levels (α_{CE}, α_{MC})
- Correlation of test statistics under H_0 and H_1
- Power (1- β =0.8)
- Allocation ratio (1:1)

Primary endpoints:

- MACE at 9 months
- Cardiac death at 9 months

	p	Δ
CE	12%	6%
MC	1.2%	0.4%

TAXUS IV trial

Sample size calculation

Using bivariate normal distribution such that

$$\min\{n|P(H_1^{CE} \cap H_1^{MC}) + P(H_1^{CE} \cap H_0^{MC}) + P(H_0^{CE} \cap H_1^{MC}) \geq 1 - \beta\}$$

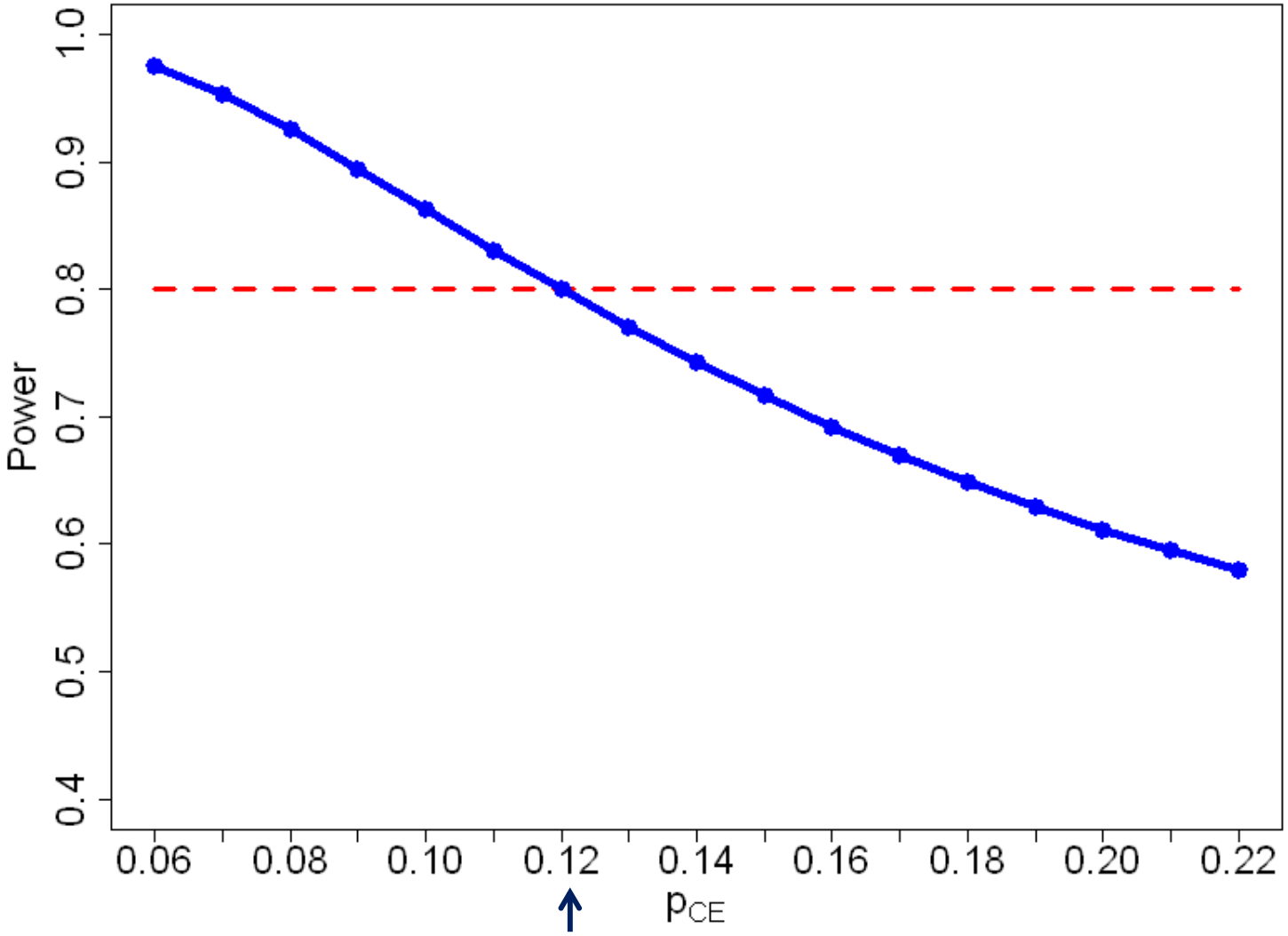
Correlation of test statistics under H_1

$$Corr(\chi^2_{CE}, \chi^2_{MC}) \approx Cov(\chi^2_{CE}, \chi^2_{MC})$$

$$Cov(\chi^2_{CE}, \chi^2_{MC}) = \frac{p^C_{MC}(1-p^C_{CE}) + p^I_{MC}(1-p^I_{CE})}{\sqrt{p^C_{CE}(1-p^C_{CE}) + p^I_{CE}(1-p^I_{CE})}\sqrt{p^C_{MC}(1-p^C_{MC}) + p^I_{MC}(1-p^I_{MC})}}$$

(Rauch and Kieser 2013)

Power – clinical trial example (continued)



TAXUS IV
(n=1090)

Assumptions:

$p_{CE} = 0.12$,

$\boldsymbol{\Delta_{CE} = 0.06}$,

$\boldsymbol{p^{C}_{MC} = 0.014}$,

$\boldsymbol{p^{I}_{MC} = 0.010}$,

$corr_{H_0} = 0.284$,

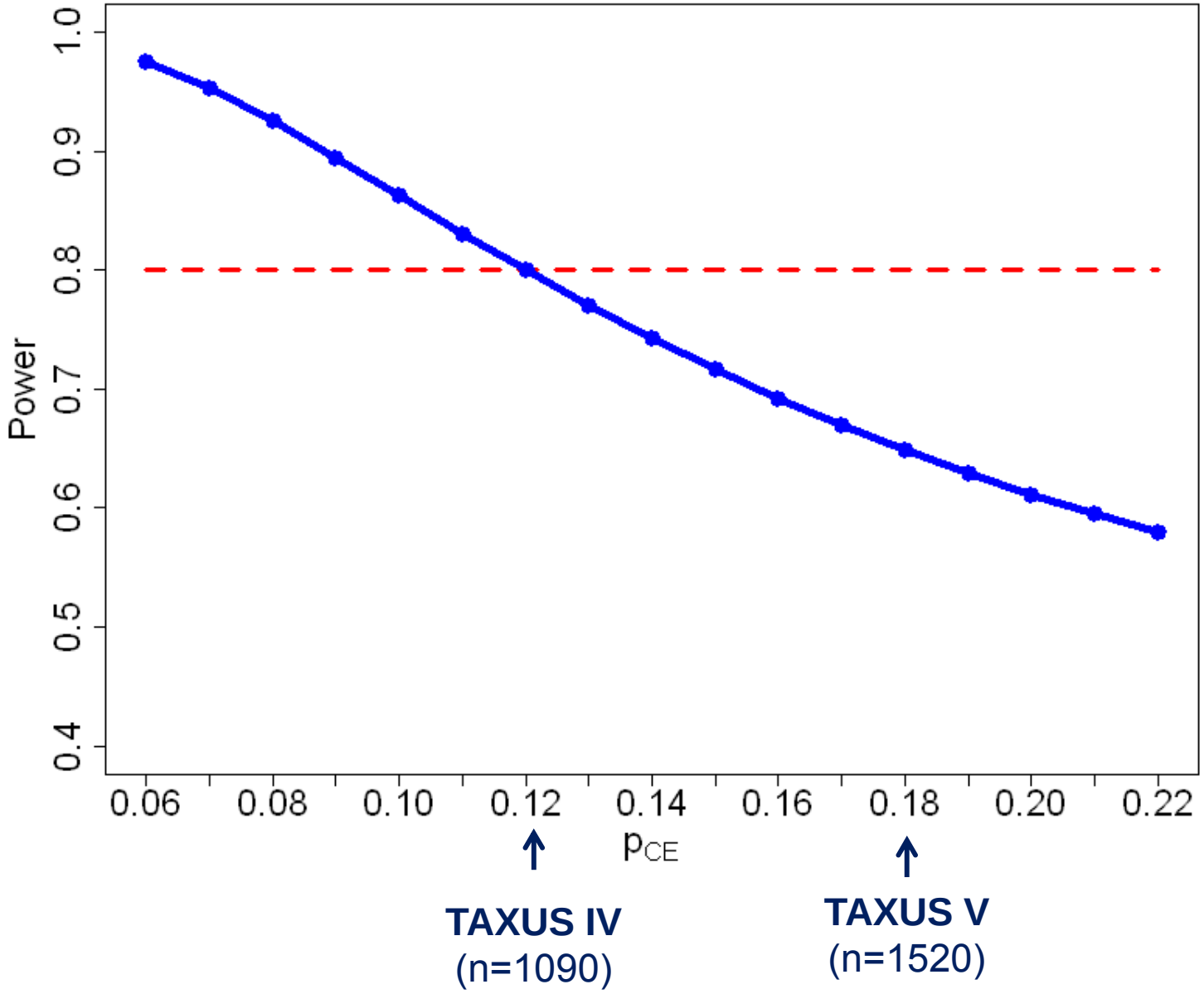
$corr_{H_1} = 0.298$,

$\alpha_{CE} = 0.0133$,

$\boldsymbol{\alpha_{MC} = 0.0125}$

→ $n_0 = 1090$

Power – clinical trial example (continued)



Assumptions:

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$\boldsymbol{p^{C}_{MC} = 0.014}$,

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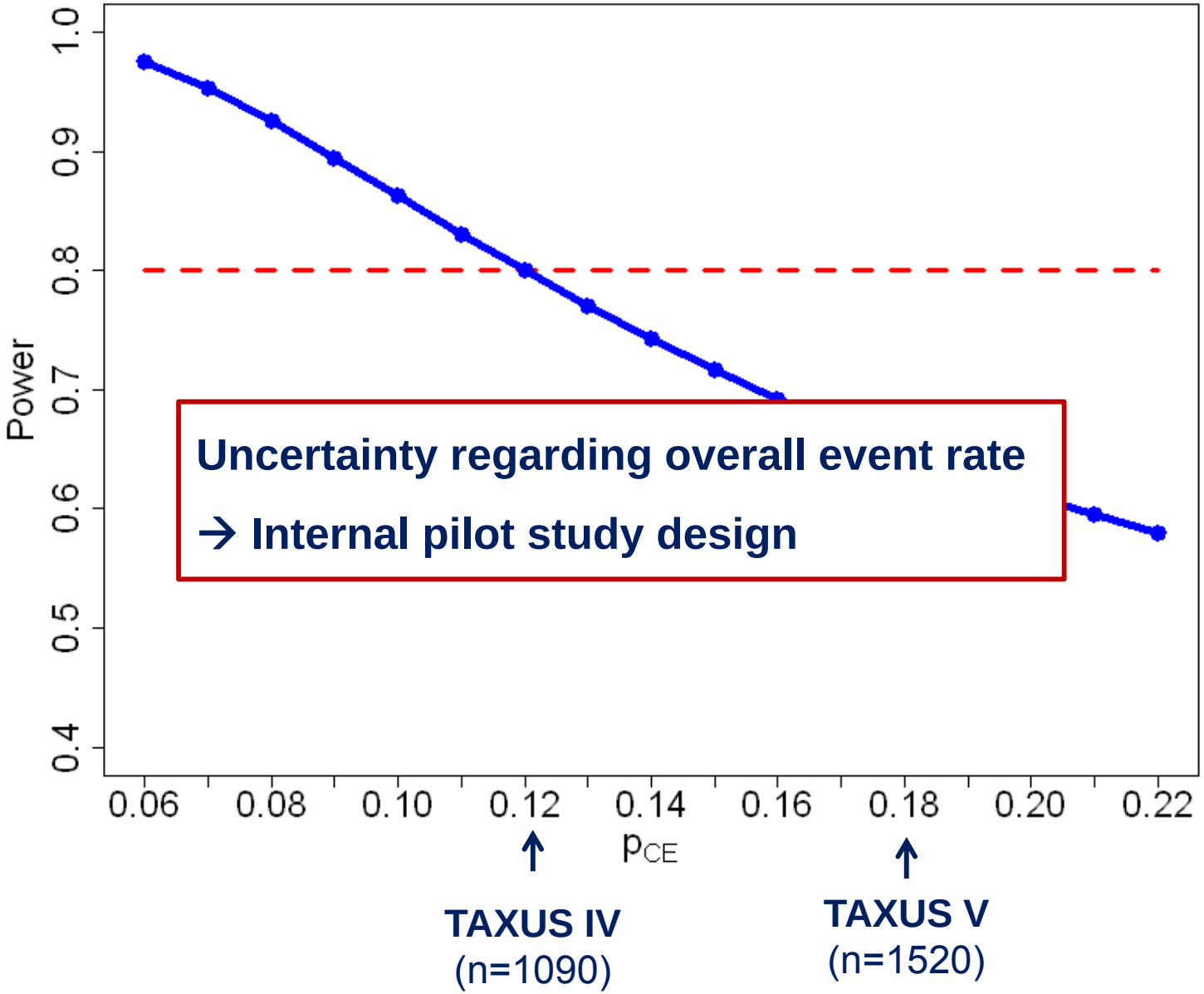
→ $n_0 = 1090$

Power – clinical trial example (continued)



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→ $n_0 = 1090$

Internal pilot study (IPS) design

Initial assumptions

Calculation of initial sample size n_0

n_1 patients

Estimation of overall event rate and correlation

Sample size recalculation
(with re-adjusted alpha levels)

n_2 patients

Final analysis

Maintain blinding

Control Type I error

$$p_{CE}^{blind} = \frac{x_{CE}^{C} + x_{CE}^{I}}{n_1}$$

$$p_{MC}^{blind} = \frac{x_{MC}^{C} + x_{MC}^{I}}{n_1}$$

Based on all patients
(n_1+ n_2)

Type I error - fixed design

Combination of binomial distribution functions:

$$\alpha^{act} = \sum_{x_{MC}^C=0}^{n^C} \sum_{x_{MC}^I=0}^{n^I} \sum_{x_{CE}^C=x_{MC}^C}^{n^C} \sum_{x_{CE}^I=x_{MC}^I}^{n^I} \binom{n^C}{x_{MC}^C} \binom{n^I}{x_{MC}^I} \binom{n^C}{x_{CE}^C - x_{MC}^C} \binom{n^I}{x_{CE}^I - x_{MC}^I}$$

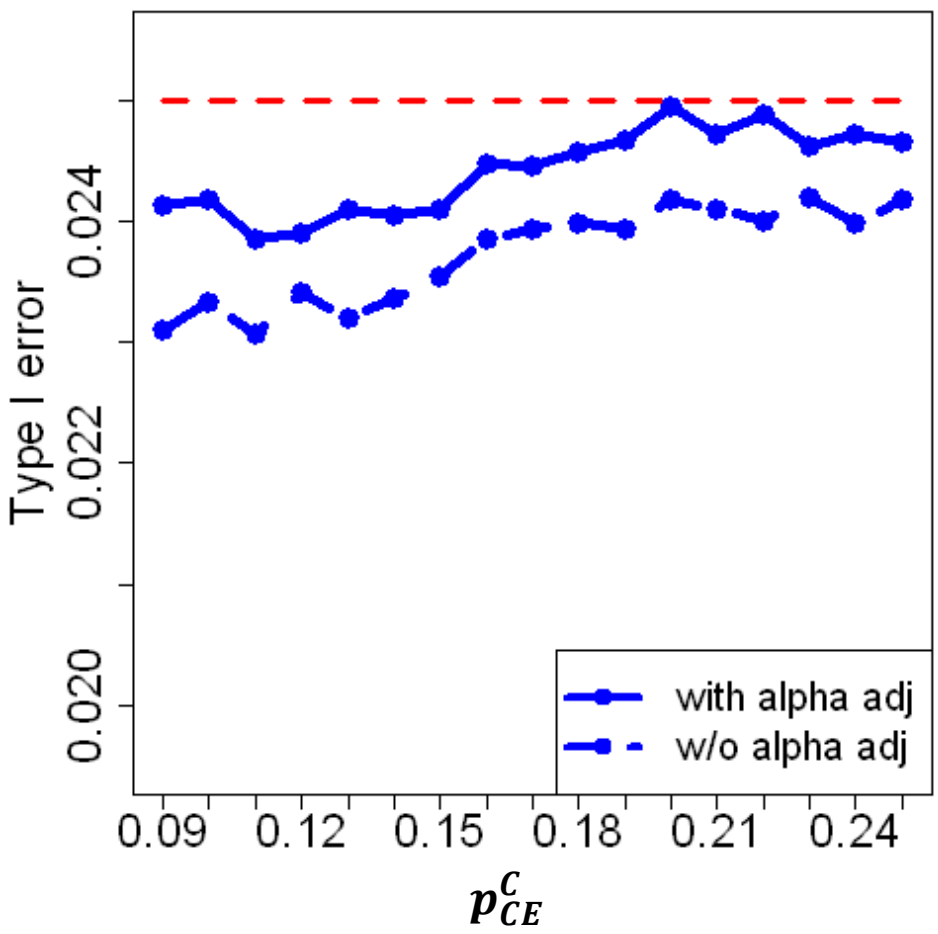
$$(p_{MC})^{x_{MC}} \cdot (1-p_{MC})^{n^C - x_{MC}^C + n^I - x_{MC}^I} \cdot (p_{CE} - p_{MC})^{x_{CE} - x_{MC}} \cdot (1 - p_{CE} + p_{MC})^{n^C + n^I - x_{CE} + x_{MC}}$$

$$I_{\{\chi^2_{CE} \geqslant \chi^2_{1,1-\alpha_{CE}}\} \cup \{\chi^2_{MC} \geqslant \chi^2_{1,1-\alpha_{MC}}\}}$$

Type I error (calculated) - fixed design

Clinical trial example:

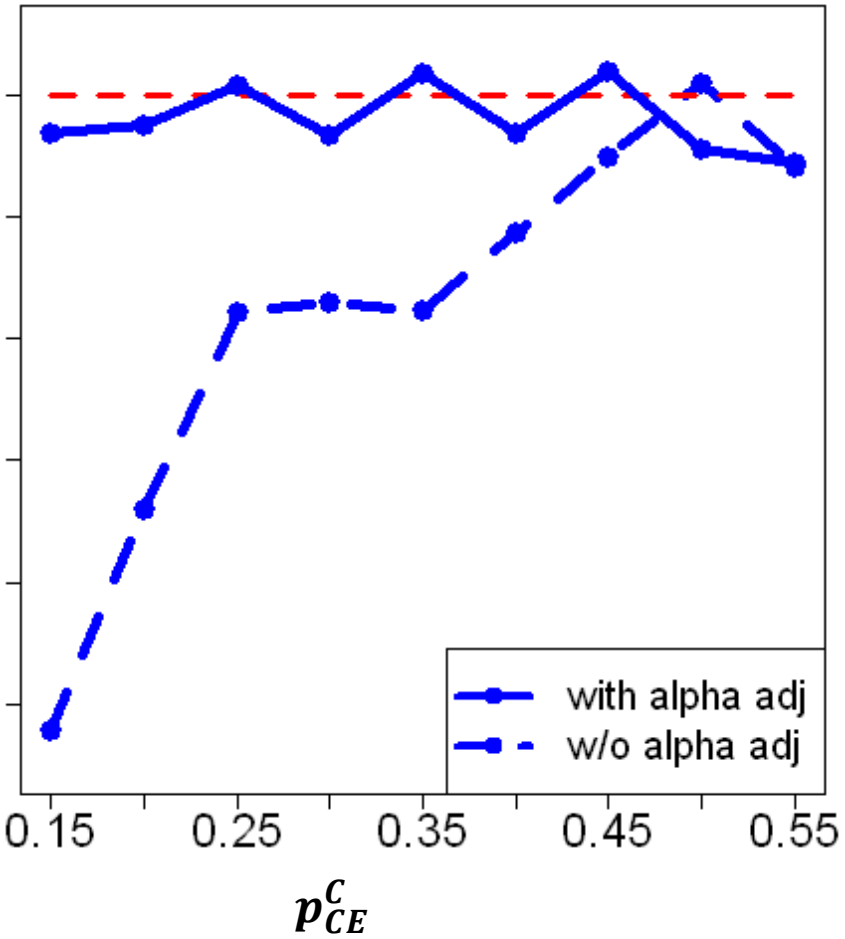
$\Delta_{CE} = 0.06,\ p^C_{MC} = 0.014,\ p^I_{MC} = 0.01$



n_0 582 846 1090 1316 1520 1706

Scenario 2:

$\Delta_{CE} = 0.1,\ p^C_{MC} = 0.1,\ p^I_{MC} = 0.05$



310 524 616 650 652

Type I error – IPS design

$$\alpha_{recalc}^{act} = \sum_{x_{MC,1}^C=0}^{n_1^C} \sum_{x_{MC,1}^I=0}^{n_1^I} \sum_{x_{CE,1}^C=x_{MC,1}^C}^{n_1^C} \sum_{x_{CE,1}^I=x_{MC,1}^I}^{n_1^I} \sum_{x_{MC,2}^C=0}^{n_2^C} \sum_{x_{MC,2}^I=0}^{n_2^I} \sum_{x_{CE,2}^C=x_{MC,2}^C}^{n_2^C} \sum_{x_{CE,2}^I=x_{MC,2}^I}^{n_2^I}$$

$$\binom{n_1^C}{x_{MC,1}^C} \binom{n_1^I}{x_{MC,1}^I} \binom{n_1^C}{x_{CE,1}^C - x_{MC,1}^C} \binom{n_1^I}{x_{CE,1}^I - x_{MC,1}^I}$$

$$\times \binom{n_2^C}{x_{MC,2}^C} \binom{n_2^I}{x_{MC,2}^I} \binom{n_2^C}{x_{CE,2}^C - x_{MC,2}^C} \binom{n_2^I}{x_{CE,2}^I - x_{MC,2}^I}$$

$$(p_{MC})^{x_{MC}} \cdot (1-p_{MC})^{n^C+n^I-x_{MC}} \cdot (p_{CE}-p_{MC})^{x_{CE}-x_{MC}} \cdot (1-p_{CE}+p_{MC})^{n^C+n^I-x_{CE}+x_{MC}}$$

$$I_{\{x_{CE}^2 \geqslant x_{1,1-\alpha_{CE}}^2\} \cup \{x_{MC}^2 \geqslant x_{1,1-\alpha_{MC}}^2\}}$$

Precision of calculations with R

Double precision numbers with limited precision (16 decimal digits)

```
> 0.3 - 0.2
[1] 0.1

> 0.3 - 0.2 == 0.1
[1] FALSE

> (0.3 - 0.2) - 0.1
[1] -2.775558e-17
```

Package **Rmpfr** → *arbitrarily precise numbers*

Precision of calculations with R

Package **Rmpfr** → *arbitrarily precise numbers*

```
> mpfr(0.01,100)
1 'mpfr' number of precision 100 bits [1]
0.010000000000000002081668171172 17
```

```
> mpfr(1,100)/mpfr(100,100)
1 'mpfr' number of precision 100 bits [1]
0.010000000000000000000000000004
```

Fixed design: p^C_{CE}=0.5, p^C_{MC}=0.25

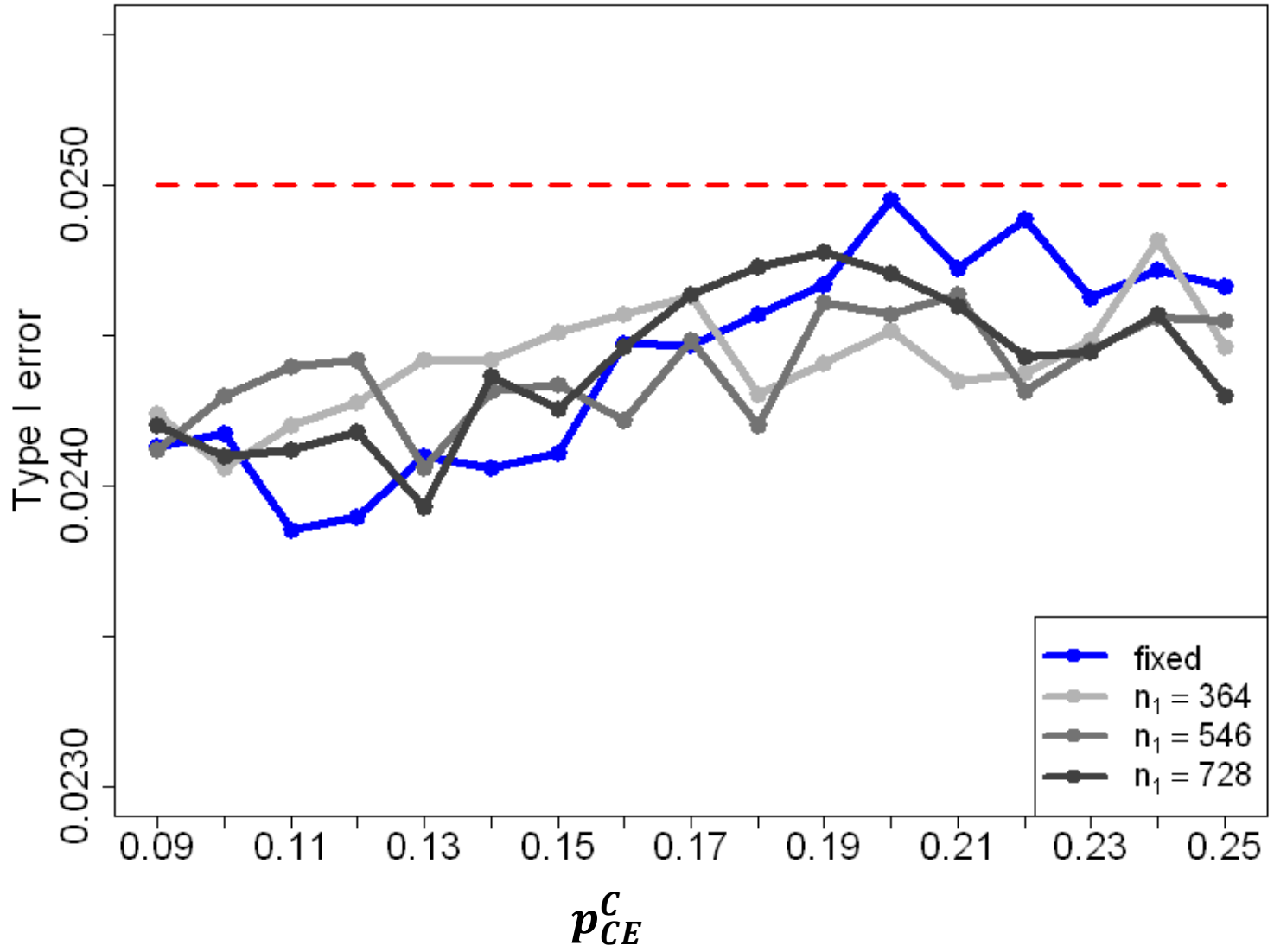
	n=120	time
standard	0.024300029706464263	~ 36 min
mpfr	0.024300029706649929825252731373 53	~ 9.6 days

Type I error - IPS, simulated vs. calculated results

p_{CE}^{C}=0.5, p_{MC}^{C}=0.25, IPS after 0.5 n

n	40	60
simulation	0.025688	0.025320
calculation	0.02568365	0.02519753
calculation time (30 cores)	1.5h	> 17h

Type I error – clinical trial example (continued)



Assumptions:

$p^C_{CE} = 0.15$,

$\boldsymbol{\Delta_{CE} = 0.06}$,

$\boldsymbol{p^C_{MC} = 0.014}$,

$\boldsymbol{p^I_{MC} = 0.010}$,

$corr_{H_0} = 0.284$,

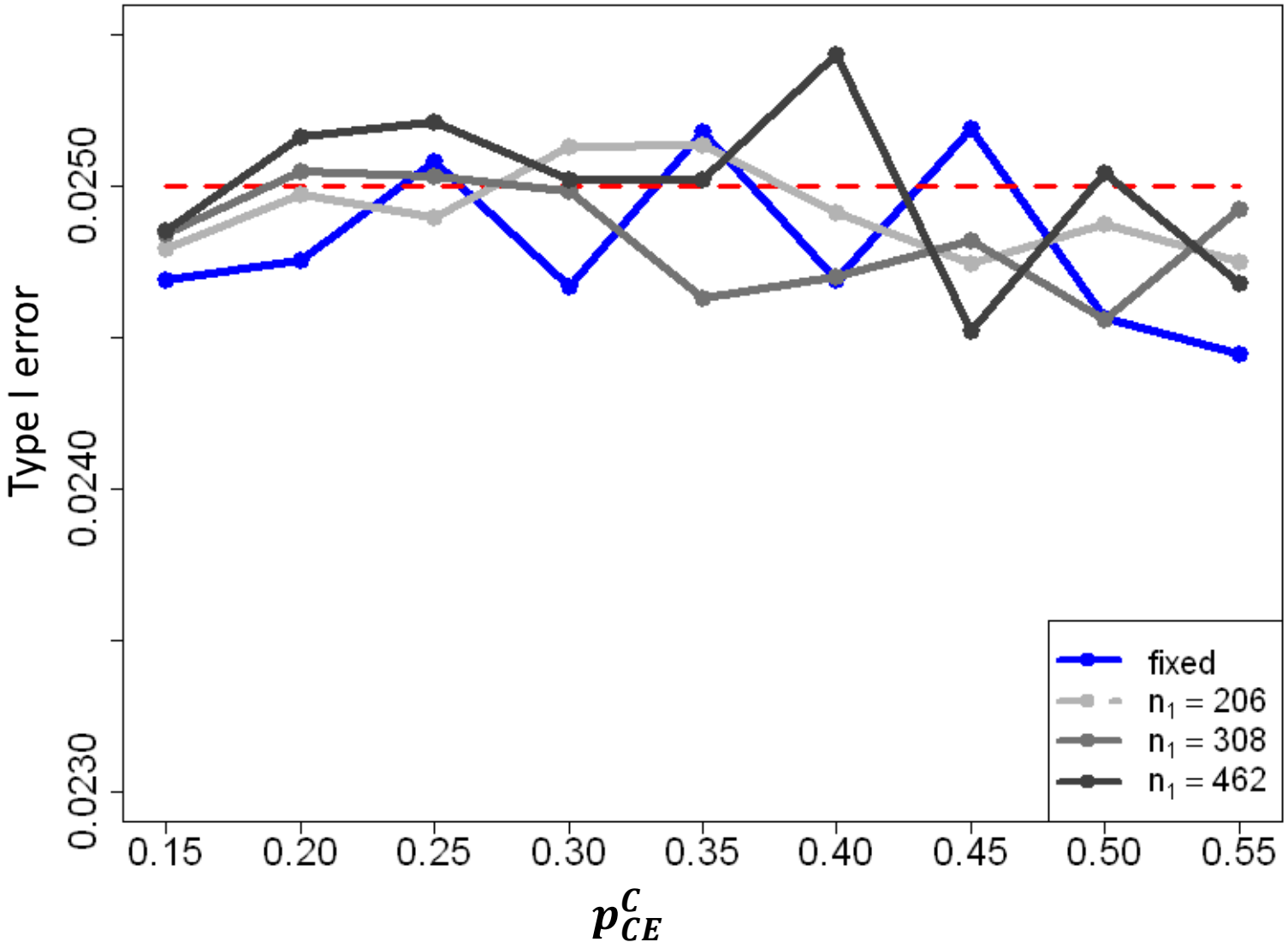
$corr_{H_1} = 0.298$,

$\alpha_{CE} = 0.0133$,

$\boldsymbol{\alpha_{MC} = 0.0125}$

$\rightarrow n_0 = 1090$

Type I error – scenario 2 (continued)



n_0	310	438	524	580	616	638	650	654	652

Assumptions:

$p^C_{CE} = 0.35$,

$\boldsymbol{\Delta_{CE} = 0.1}$,

$\boldsymbol{p^C_{MC} = 0.1}$,

$\boldsymbol{p^I_{MC} = 0.05}$,

$corr_{H_0} = 0.454$,

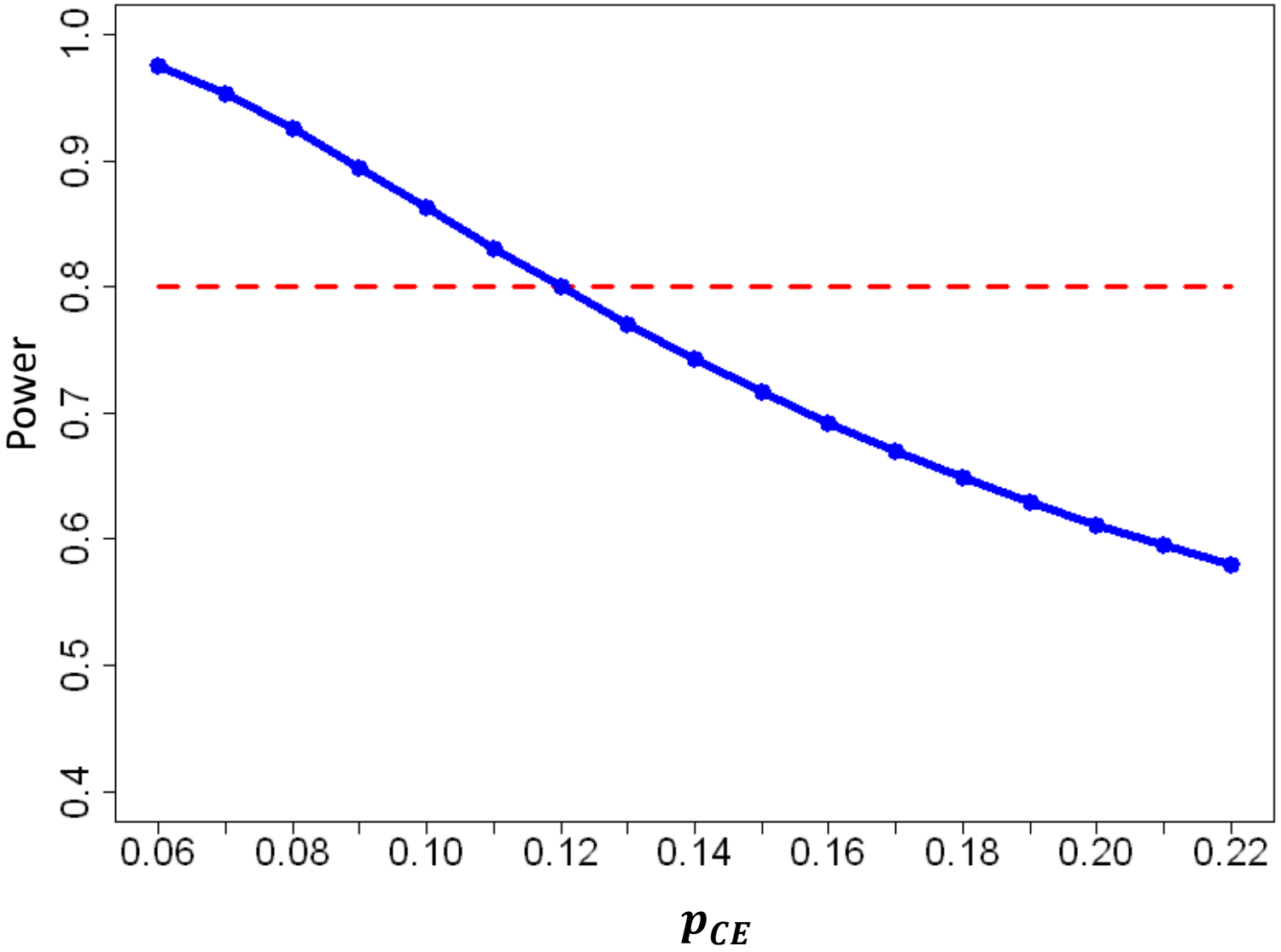
$corr_{H_1} = 0.429$,

$\alpha_{CE} = 0.0141$,

$\boldsymbol{\alpha_{MC} = 0.0125}$

$\rightarrow n_0 = 616$

Power – clinical trial example (continued)



n_0	582	760	930	1090	1242	1386	1520	1646	1762

Assumptions:

$p_{CE} = 0.12$,

$\boldsymbol{\Delta_{CE} = 0.06}$,

$\boldsymbol{p^C_{MC} = 0.014}$,

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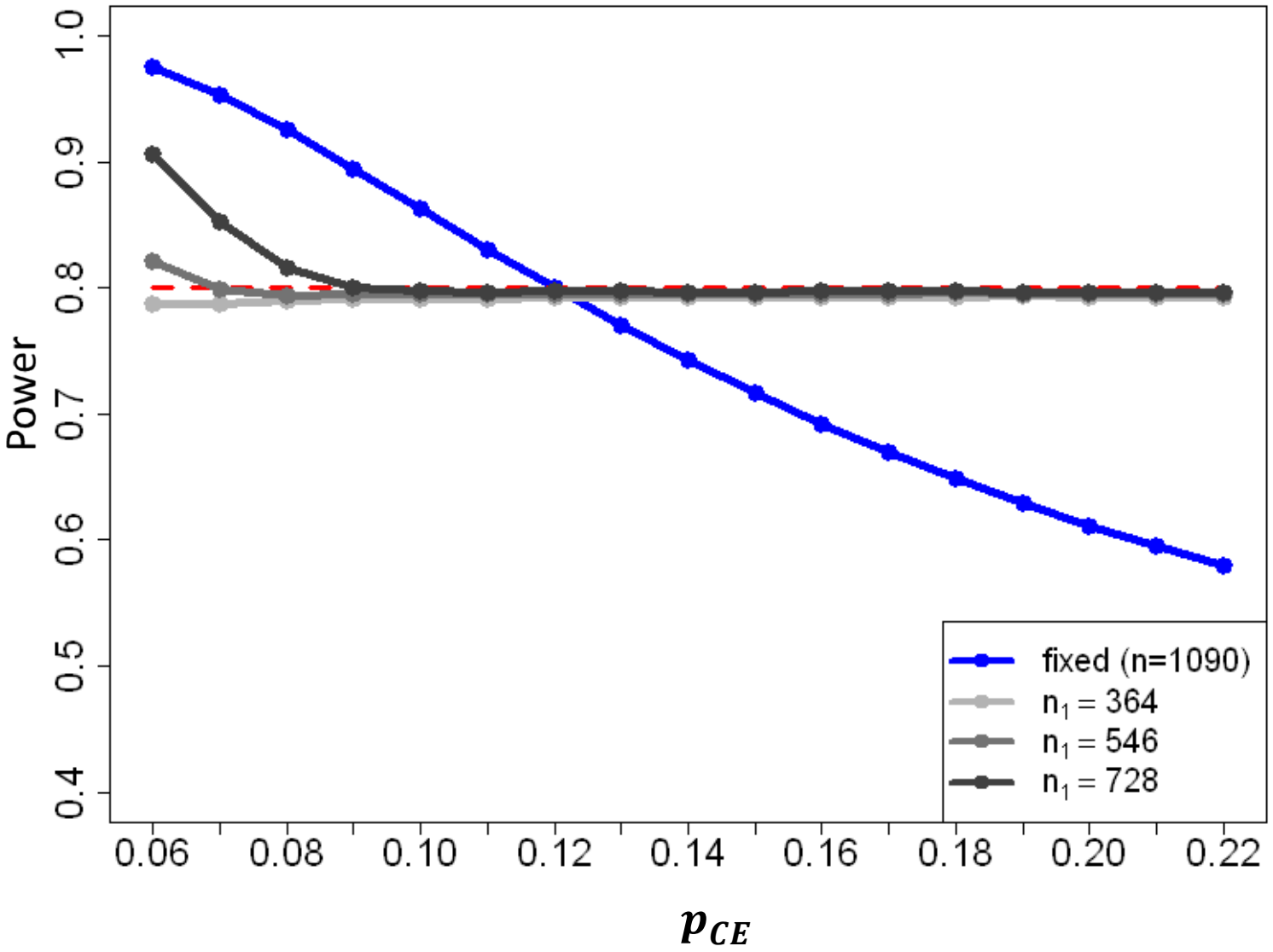
Power – clinical trial example (continued)



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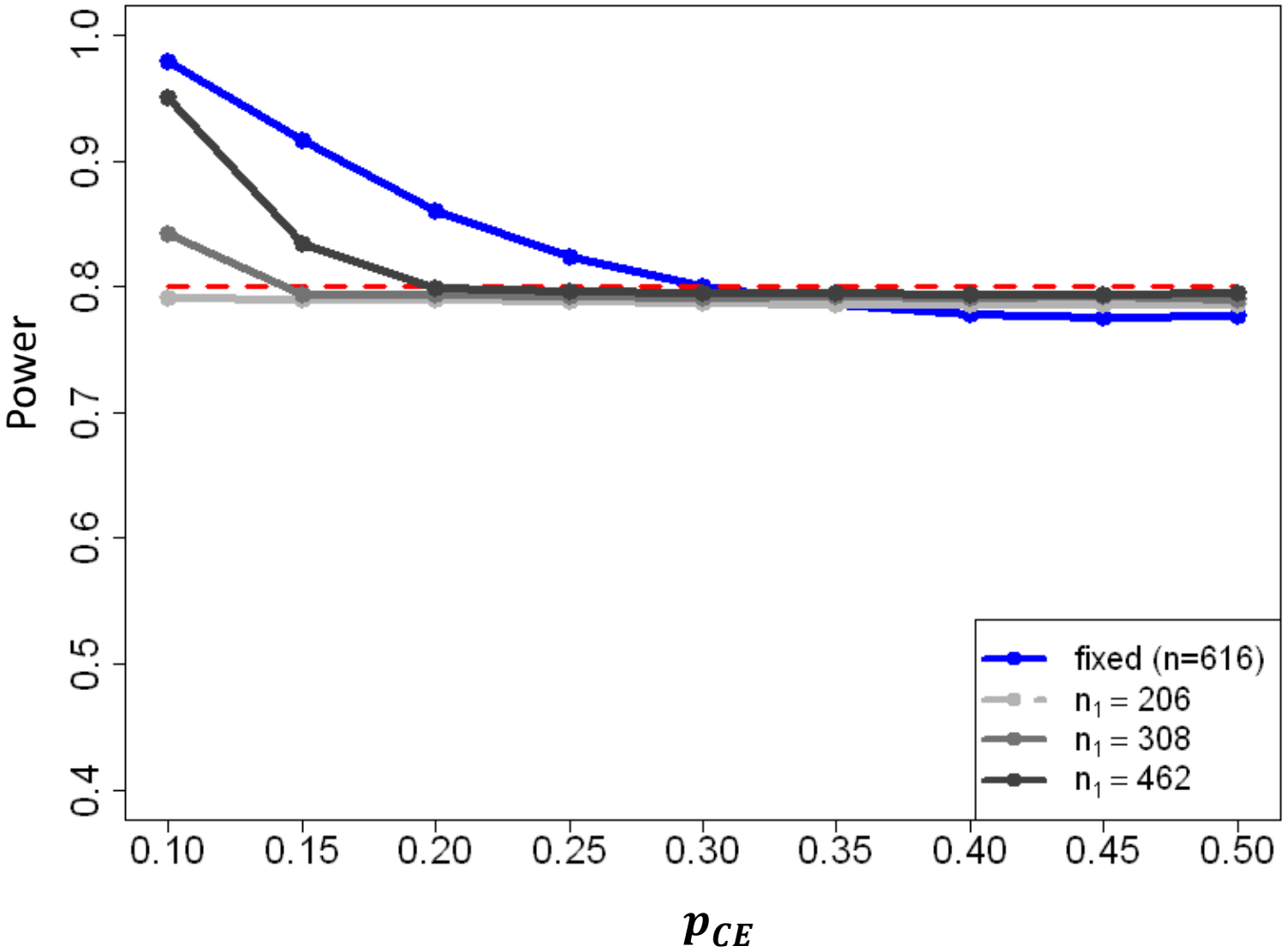
Power – scenario 2 (continued)



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$\boldsymbol{p^I_{MC} = 0.05}$,

$corr_{H_0} = 0.454$,

$corr_{H_1} = 0.429$,

$\alpha_{CE} = 0.0141$,

$\boldsymbol{\alpha_{MC} = 0.0125}$

→ $n_0 = 616$

Summary

- IPS robust against missspecifications of overall event rate
- Fixed and IPS design seem to be very similar regarding Type I error
- Small overall event rates and relatively small IPS

  → Power not reached

Outlook

- Application of correction factor
- Changes in scenarios:
  - Restricted sample size recalculation
  - Alpha splitting
  - Allocation ratio/ unequal group sizes
  - Multiplicity adjustment
  - …
- Generalization to *k* endpoints (continuous/binary)

Literatur

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