AN INTRODUCTION TO ADAPTIVE DESIGNS

Group sequential designs and early stopping in clinical trials

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Outline

- Definitions
- Operational considerations
- Group sequential designs
- Efficacy stopping boundaries
- Futility stopping boundaries
- Alpha-spending approach

Definition(s)

European Medicines Agency

London, 18 October 2007
Doc. Ref. CHMP/EWP/2459/02

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

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Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018
Clinical/Medical

Definition(s)

- A study design is called "*adaptive*" if statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an **interim analysis** with full **control of the type I error**. (EMA, 2007)

- An *adaptive design* is defined as a clinical trial design that allows for **prospectively planned** modifications to one or more aspects of the design based on **accumulating data** from subjects in the trial. (FDA, 2018)

Why adaptive designs?

- **Ethical** : Ensure subjects are not exposed to unsafe, inferior or innefective treatments

- **Administrative** : Ensure the trial is conducted as planned (correct population, eligibility criteria)

- **Economical** : Exploit a new treatment earlier if a positive result is observed. Save resources if negative result is observed.

Interim Analysis

- Any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to the formal completion of a trial (ICH E9, 1998)

- Any examination of data obtained from subjects in a trial while that trial is ongoing, and is not restricted to cases in which there are formal between-group comparisons (FDA, 2018)

Unblinding of interim results

- Usually requires **unblinding** of the data

→ Knowledge of interim results (based on comparisons of treatment groups) can change the behaviour of the investigators and subjects

- Trial integrity must be maintained
- Sponsors, investigators, subjects, people involved in the trial conduct must remain unaware of the product codes
- Confidentiality of the interim results must be ensured

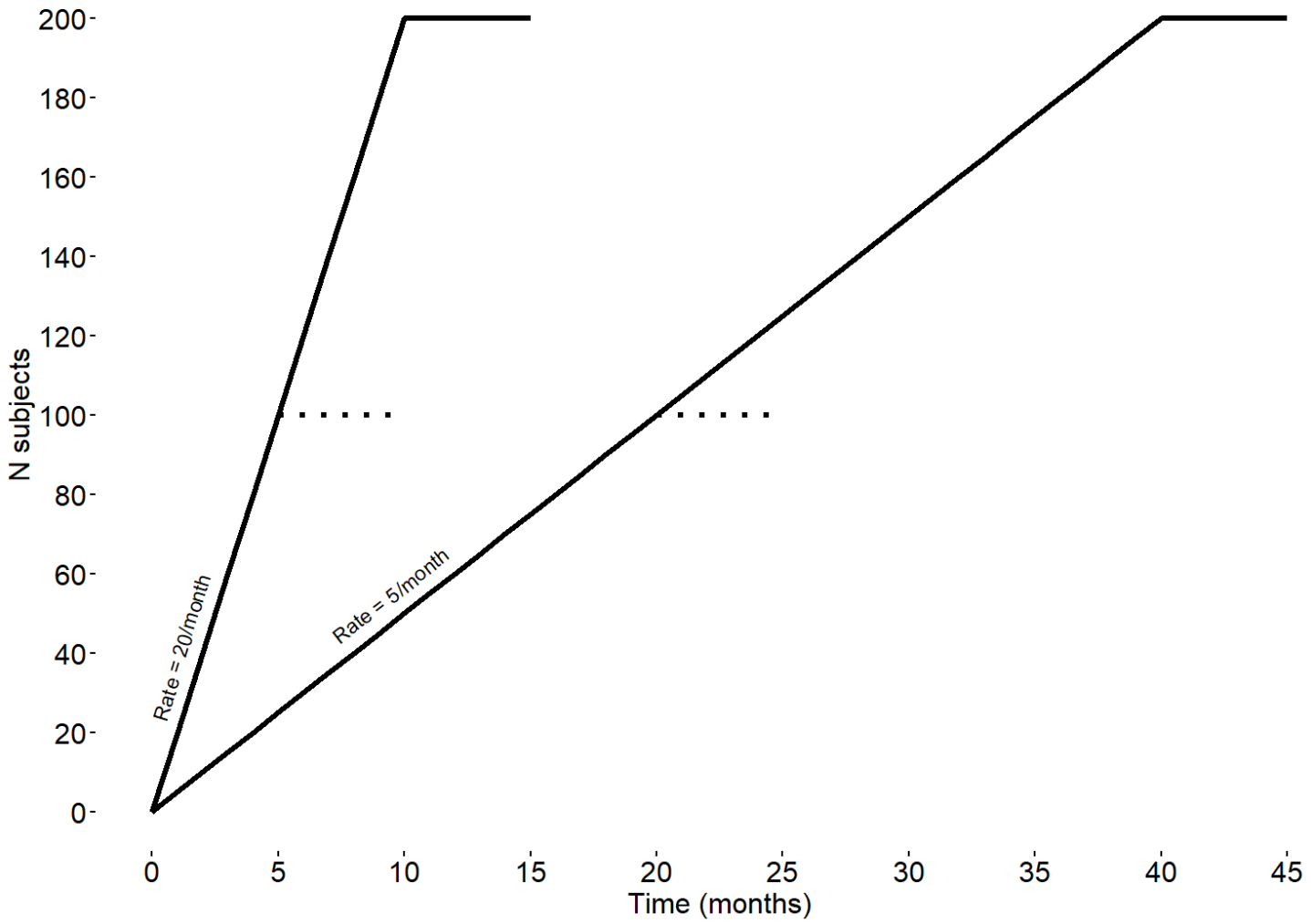
Data monitoring committee

- An independent Data Monitoring Committee (DMC) should be constitued.
  - Indepdendent group of experts mandated to review the interim results
  - At least two (independent) clinical experts and one (independent) statistician are members
  - DMC charter and interim SAP must be written
  - Provide only recommendations based on pre-planned decision rules
  - At completion of the trial only, interim results can be disclosed.
  - Can request additional analyses

Recruitment

- Sample size = 200
- Follow-up period = 5m
- Recruit. rate = 5 and 20 / m
- Interim analysis at N = 100

→ **Overrunning**



Examples of adaptive designs

a) adaptive randomization design,
b) group sequential design,
c) sample size re-estimation design,
d) drop-the-loser design,
e) adaptive dose finding (e.g., dose escalation) design,
f) biomarker-adaptive design,
g) adaptive treatment-switching design,
h) hypothesis-adaptive design,
i) adaptive seamless phase II/III trial design, and
j) multiple adaptive design.

Group sequential designs

- So-called “group sequential” designs have been developed that **avoid inflating the pre-specified type I error** associated with the repeated testing of the treatment effect based on accumulating data.(EMEA, 2007)

- Group sequential trials allow for one or more **prospectively planned interim analyses** of comparative data with **prespecified criteria for stopping the trial** (FDA, 2018)

Group sequential designs

- **What**: Look at accumulating data during the course of trial
- **Why**: Take decisions to continue or stop the trial
- **How**: K-1 interim analyses planned and one final analysis.

Maximum sample size

With K analyses planned (K-1 interim and a final analysis), and n_i observations per stage, the maximum sample size N is

$$N_{max} = n_1 + n_2 + \cdots + n_K$$

With equally sized stages,

$$N_{max} = Kn$$

Fixed design studies

- In the fixed design case the sample size is

$$N_{fix} = N_{fix}(\alpha, \beta, \Delta, \sigma)$$

- When the study is completed, compute the test statistic T and reject H_0, if (two-sided case)

$$|T| \geq z_{1-\alpha/2}$$

Inflation factor

- Monitoring data during intetrim analyses comes at cost
- The **maximum sample size gets inflated**
- It can be shown that

$$N_{max} = N_{fix} \times IF(K, \alpha, \beta)$$

- N_{fix} = sample size in fixed case
- IF = Inflation factor

Average sample size

- The maximum sample size is inflated, but the average sample size ASN is reduced

$$ASN_{H_1} = n_1 + n_2 P_{H_1}(|Z_1| < c_1) + n_3 P_{H_1}(|Z_1| < c_1, |Z_2| < c_2) + \ \ldots$$

- Group sequential designs allow to stop the trial early. → The average stopping time is decreased

Efficacy stopping boundaries

- $c_1, c_2, \ldots, c_K$ are a set of critical values corresponding to stopping boundaries.
- The trial is stopped at first interim i were $|Z_i| \geq c_i$
- To preserve the familywise error rate (FWER), i.e the probability to reject at least one true null hypothesis, c_i's must satisfy:

$$P_{H_0}(|Z_1| \geq c_1 \; or \; |Z_2| \geq c_2 \; or \; \ldots or \; |Z_K| \geq c_K) = \alpha$$

- There are different solutions.

Efficacy stopping boundaries

- Pocock (1977) proposed constant boundaries $c_i = c_P(K, \alpha)$

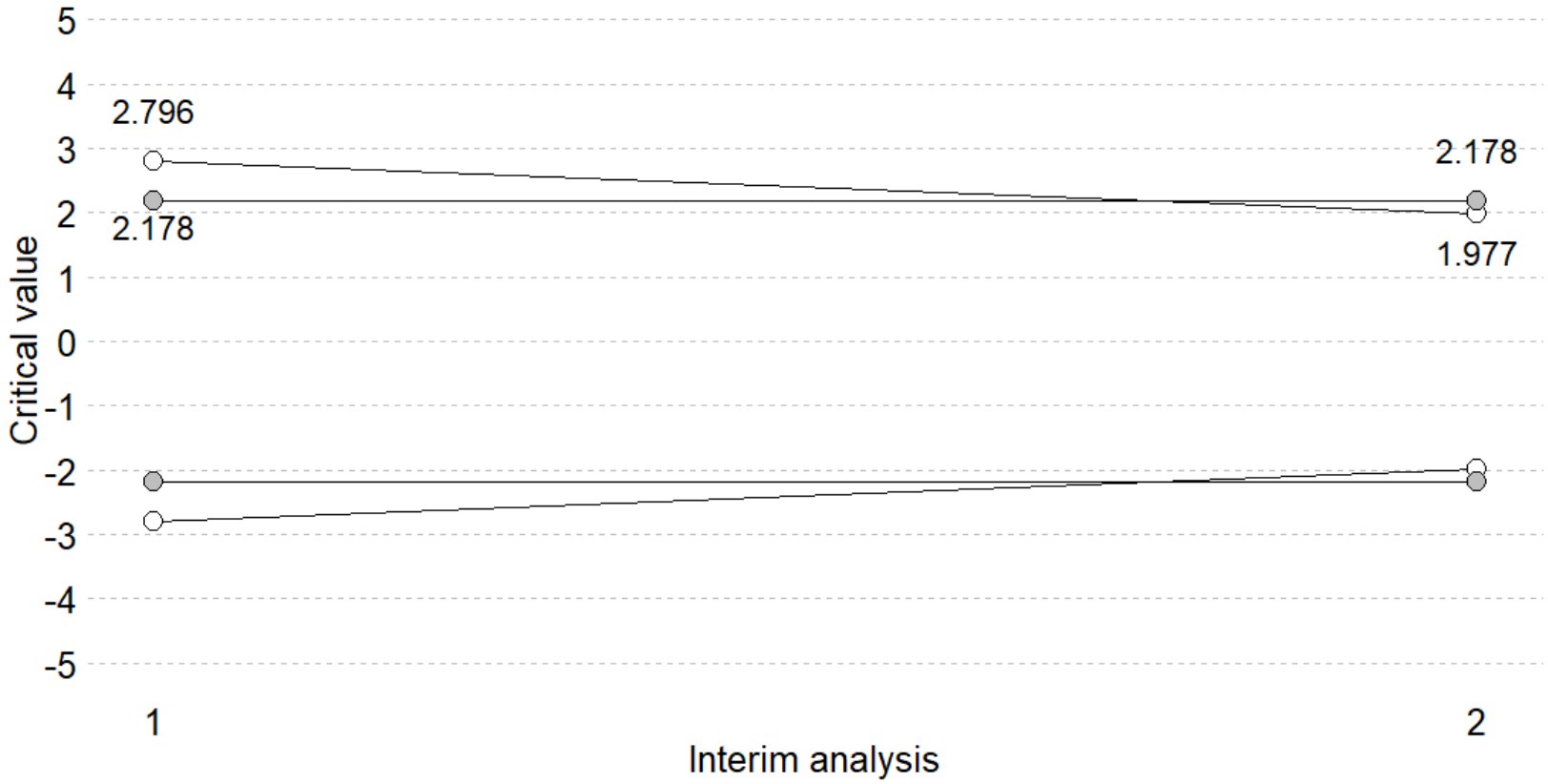
$$P_{H_0}(|Z_1| \geq c_P \; or \; |Z_2| \geq c_P \; or \; \ldots or \; |Z_K| \geq c_P) = \alpha$$

- O'Brien and Fleming (1979) proposed decreasing boundaries $c_i = \frac{c_{OBF}(K,\alpha)}{\sqrt{i}}$

$$P_{H_0}\left(|Z_1| \geq c_{OBF} \; or \; |Z_2| \geq \frac{c_{OBF}}{\sqrt{2}} \; or \; \ldots or \; |Z_K| \geq \frac{c_{OBF}}{\sqrt{K}}\right) = \alpha$$

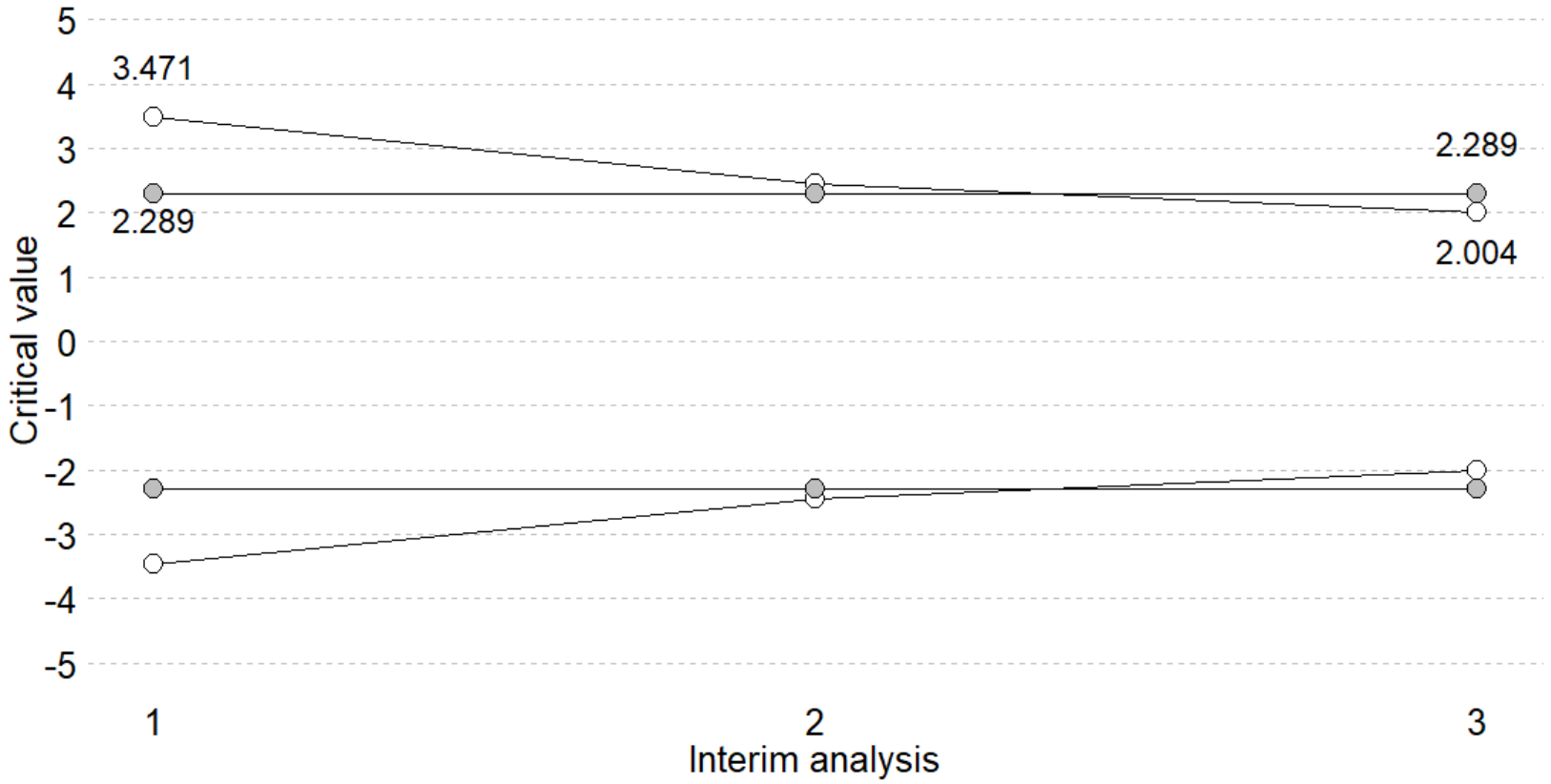
- Both methods require equally sized stages

Stopping boundaries



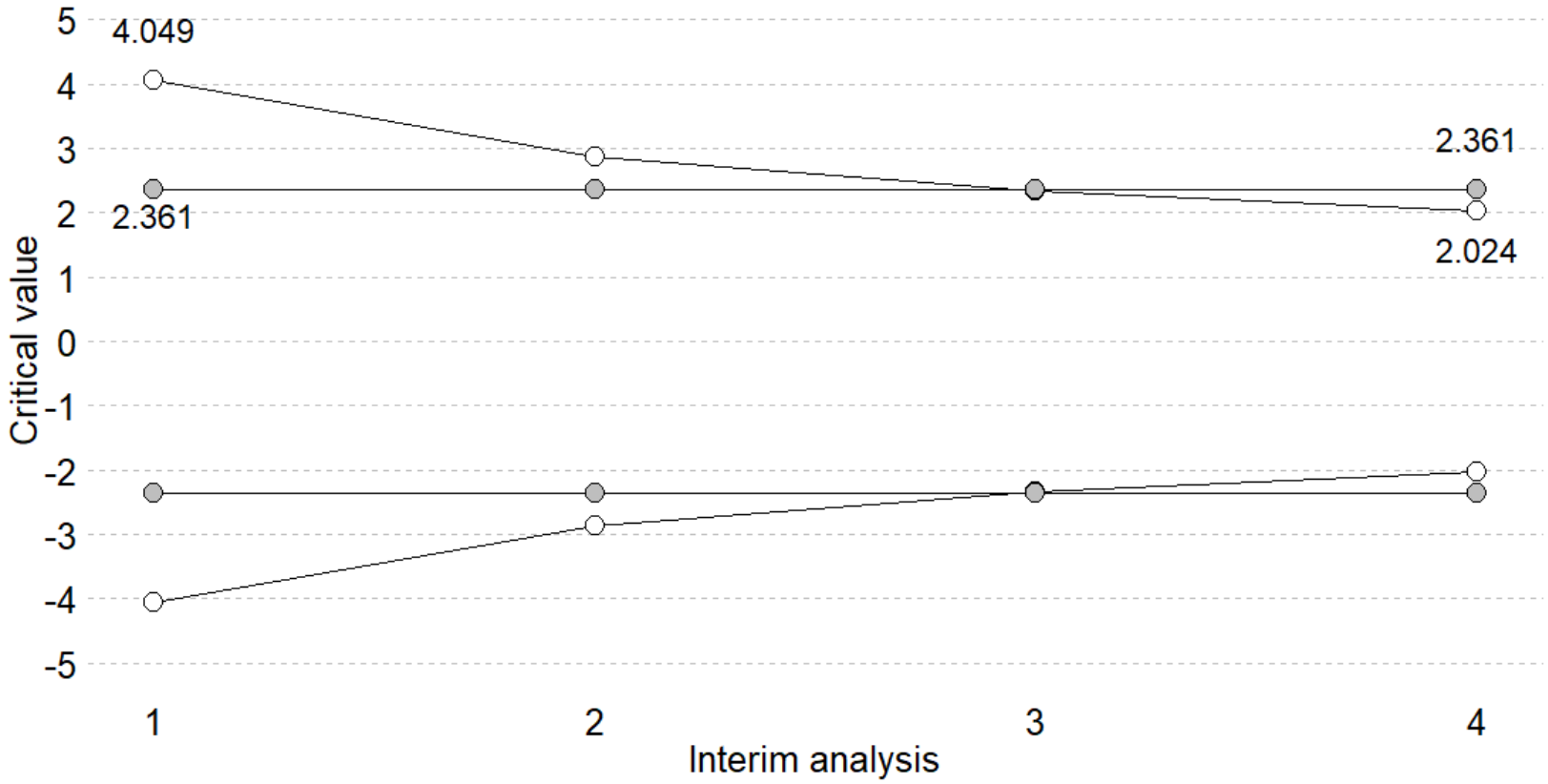
Z-value	P-value
1.977	0.0480
2.178	0.0294
2.796	0.0052

Stopping boundaries



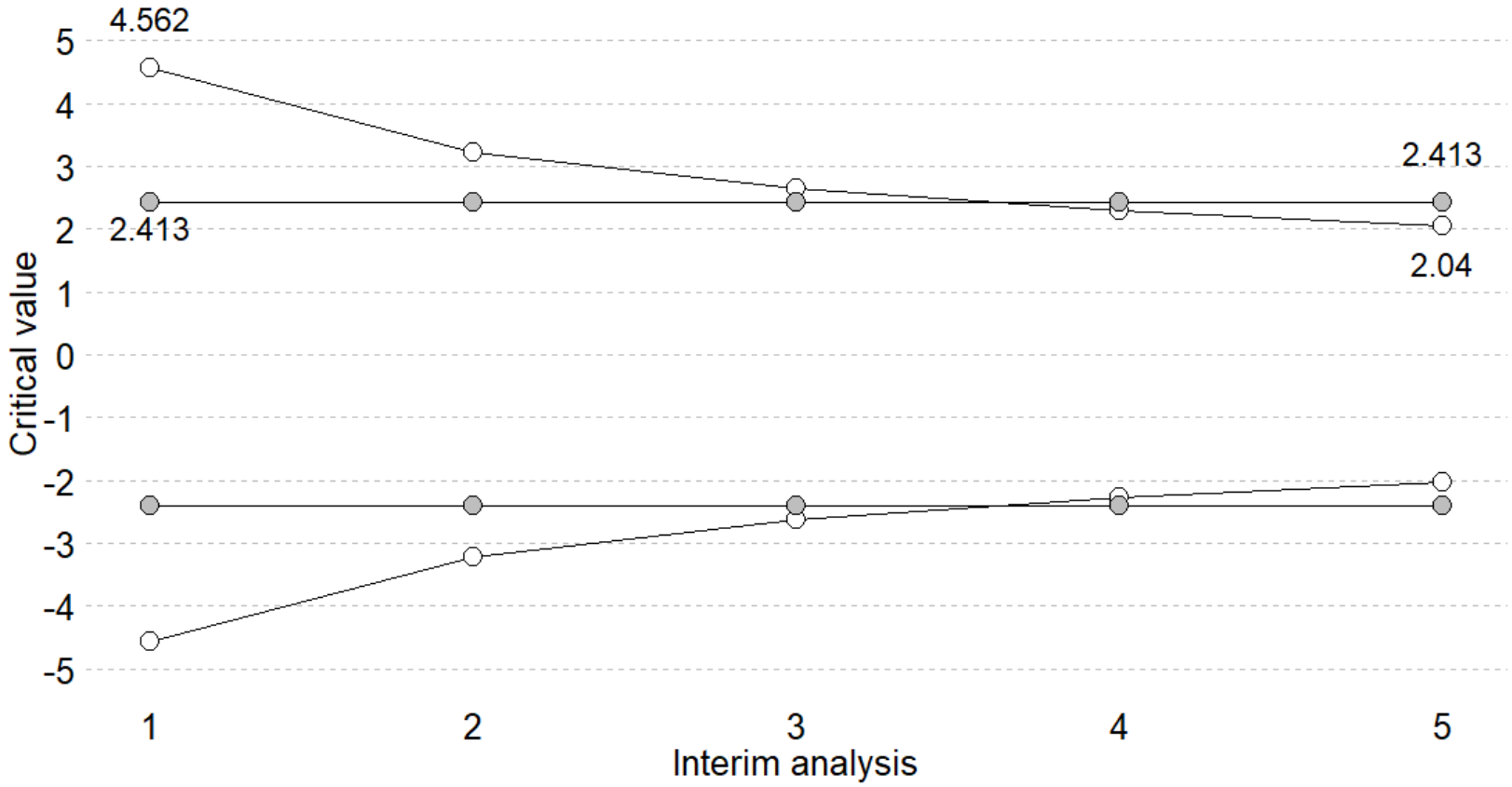
Z-value	P-value
2.004	0.0451
2.289	0.0221
3.471	0.0005

Stopping boundaries



Z-value	P-value
2.024	0.0429
2.361	0.0182
4.049	0.00005

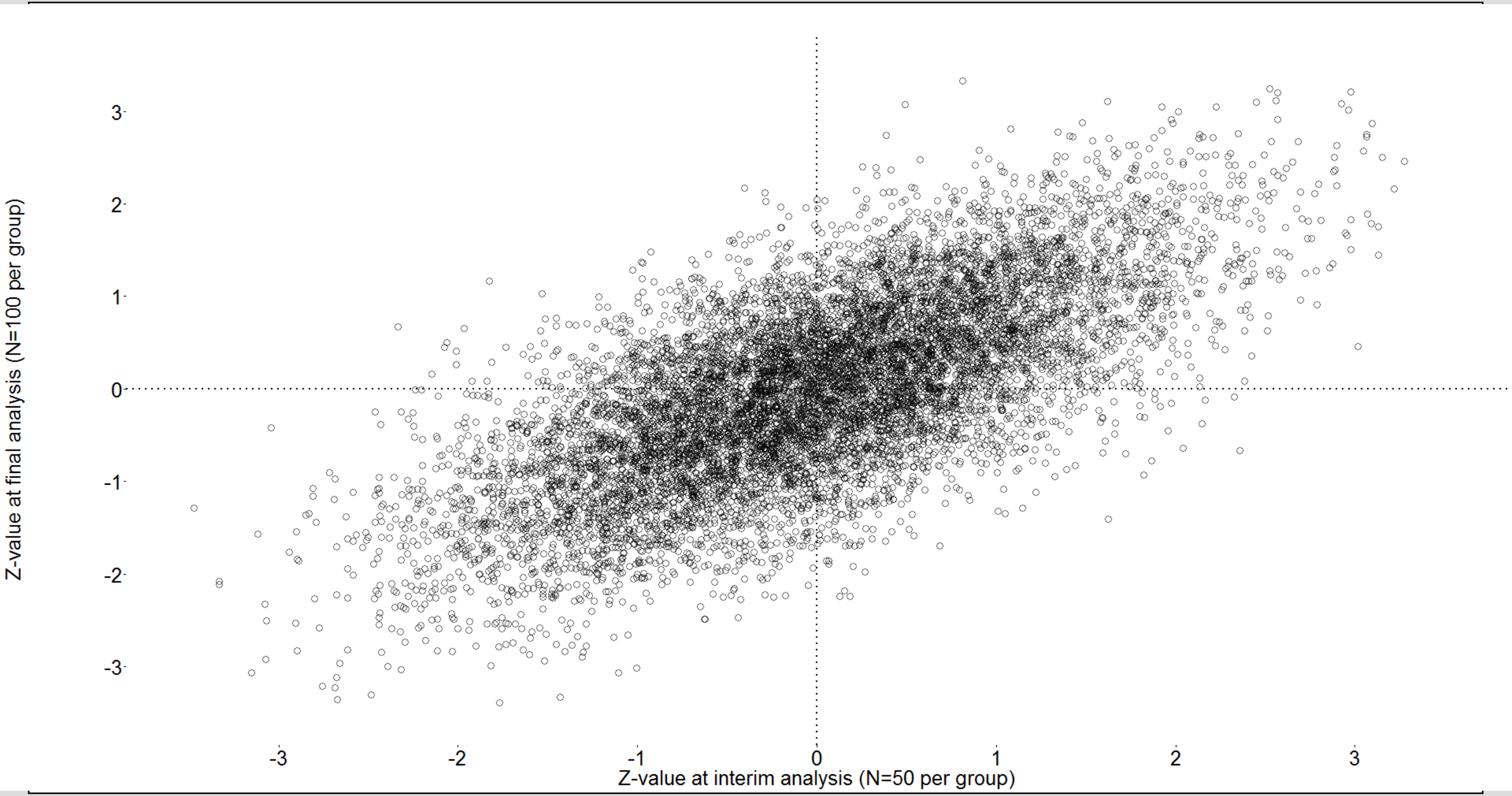
Stopping boundaries

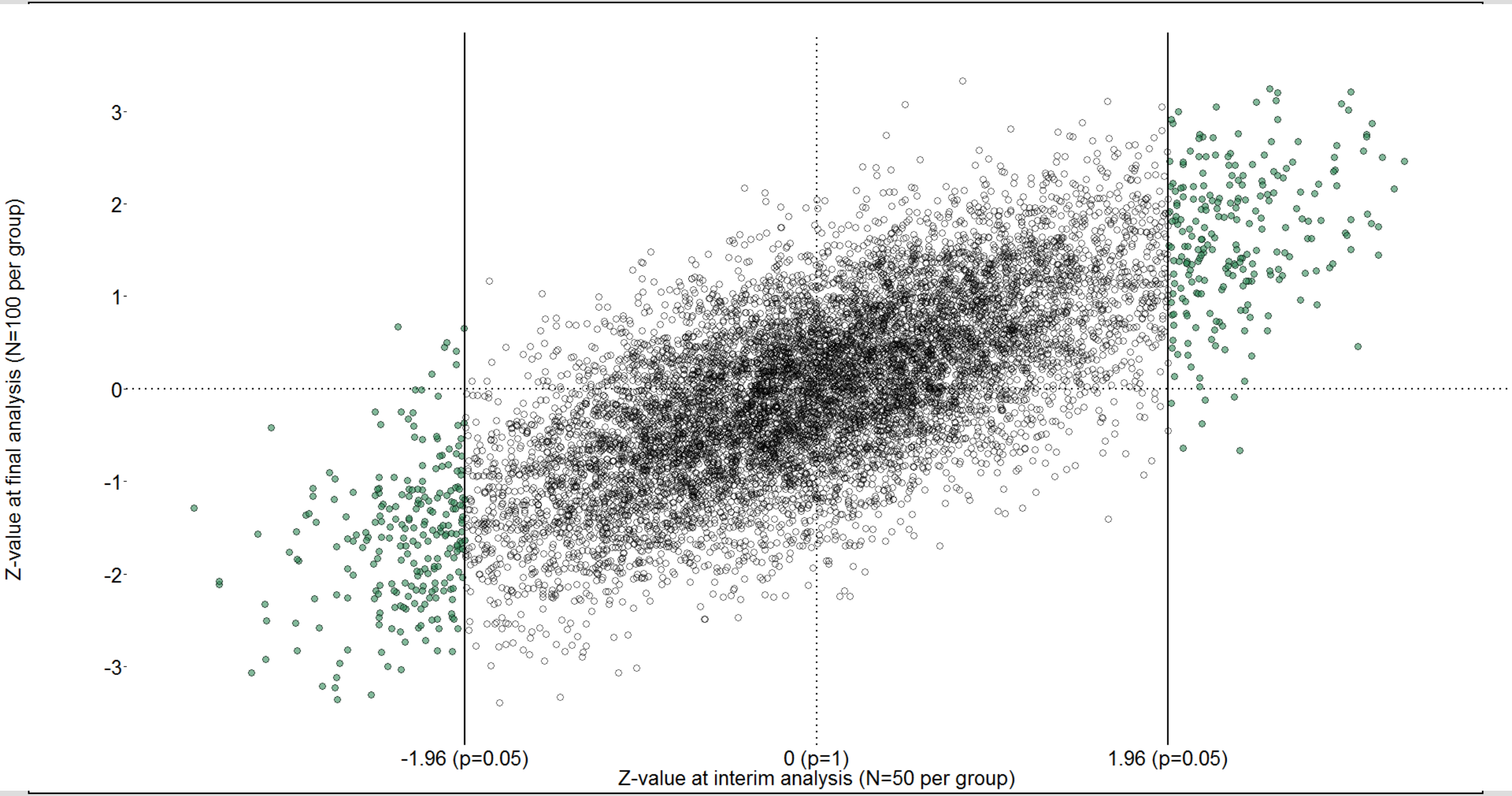


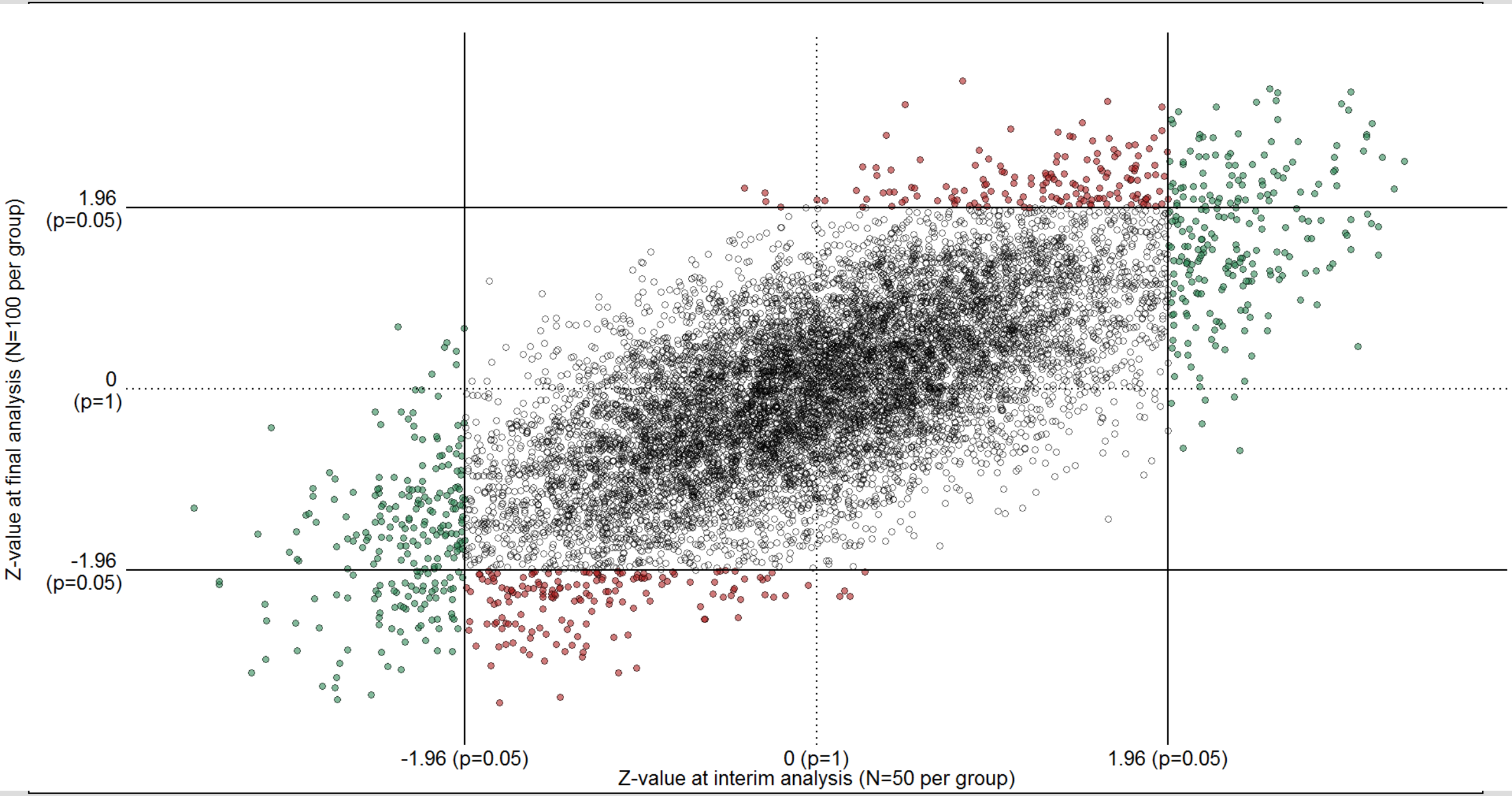
Z-value	P-value
2.04	0.04135
2.413	0.0158
4.562	0.000005

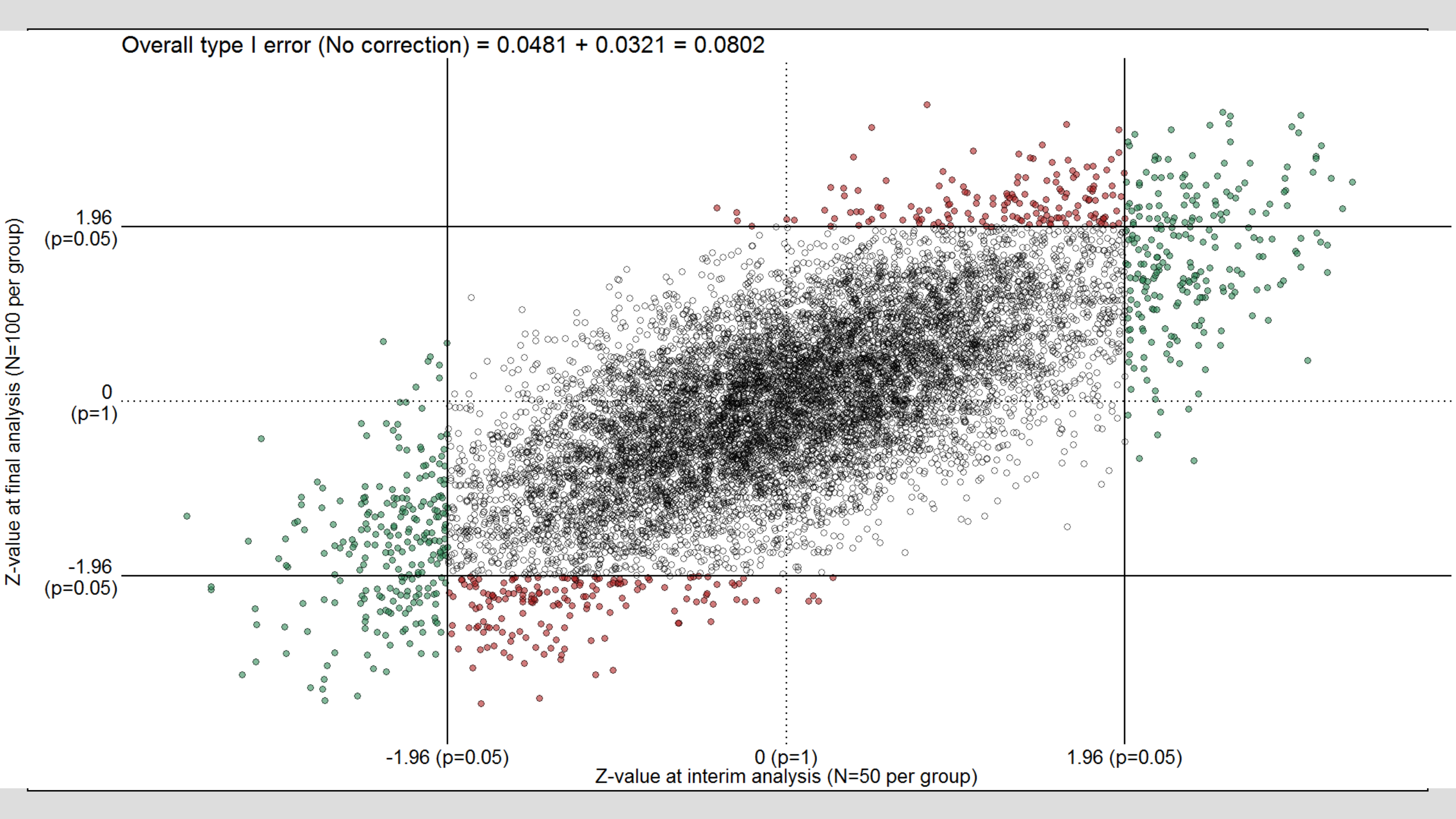
GSD – simulations

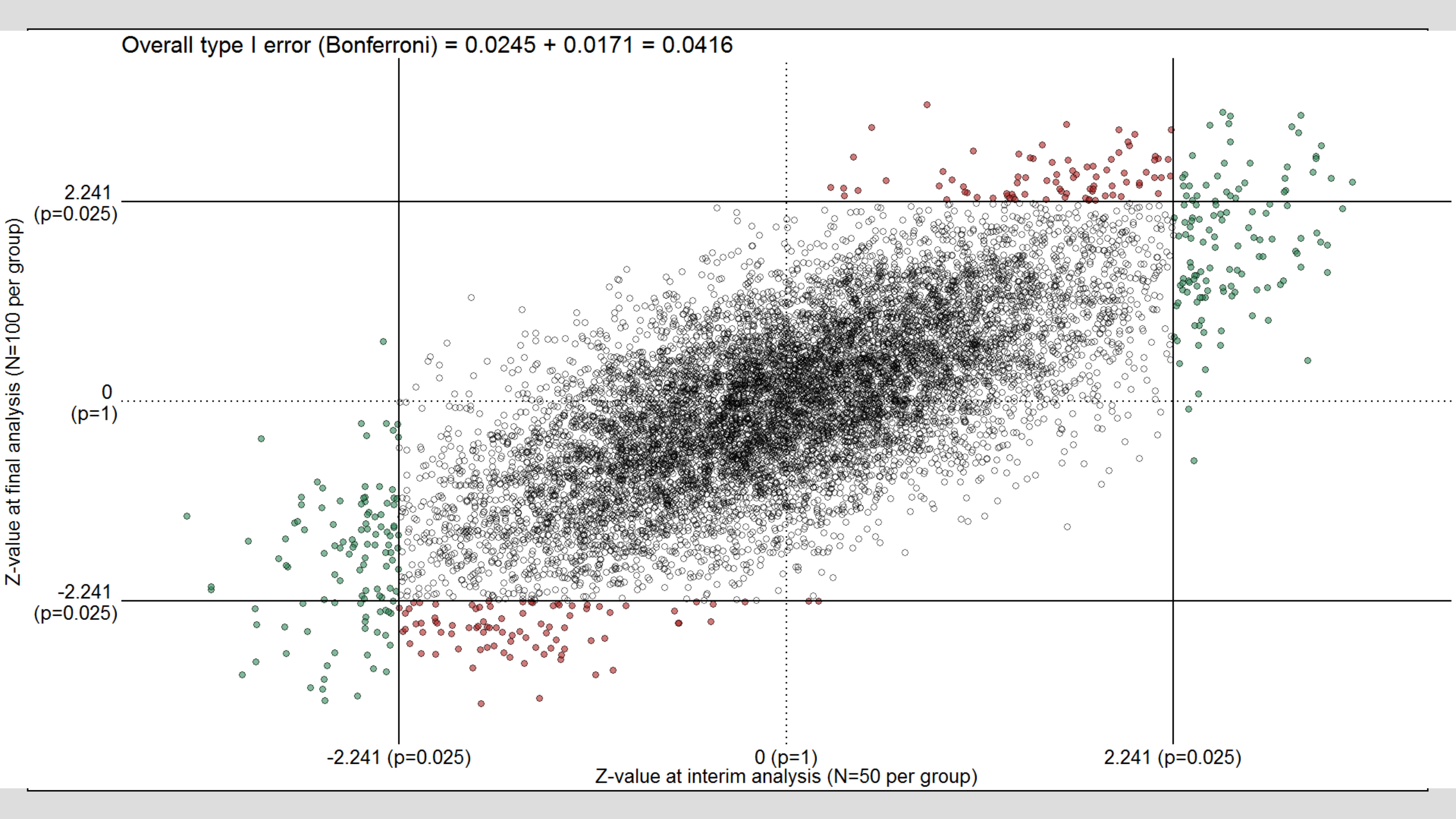
- How type I error is inflated with repeated significance testing
- Example
  - mean of treatment A : $\mu_A = 0$
  - mean of treatment B : $\mu_B = 0$
- 100 observations (subjects) in each group distributed as
  - $X_{Ai} \sim N(0,1)$
  - $X_{Bi} \sim N(0,1)$
- Hypothesis (two-sided): $H_0 : \mu_A = \mu_B$ and $H_A : \mu_A \neq \mu_B$
- Interim analysis when 50 subjects are recruited in each group
- 10’000 replications

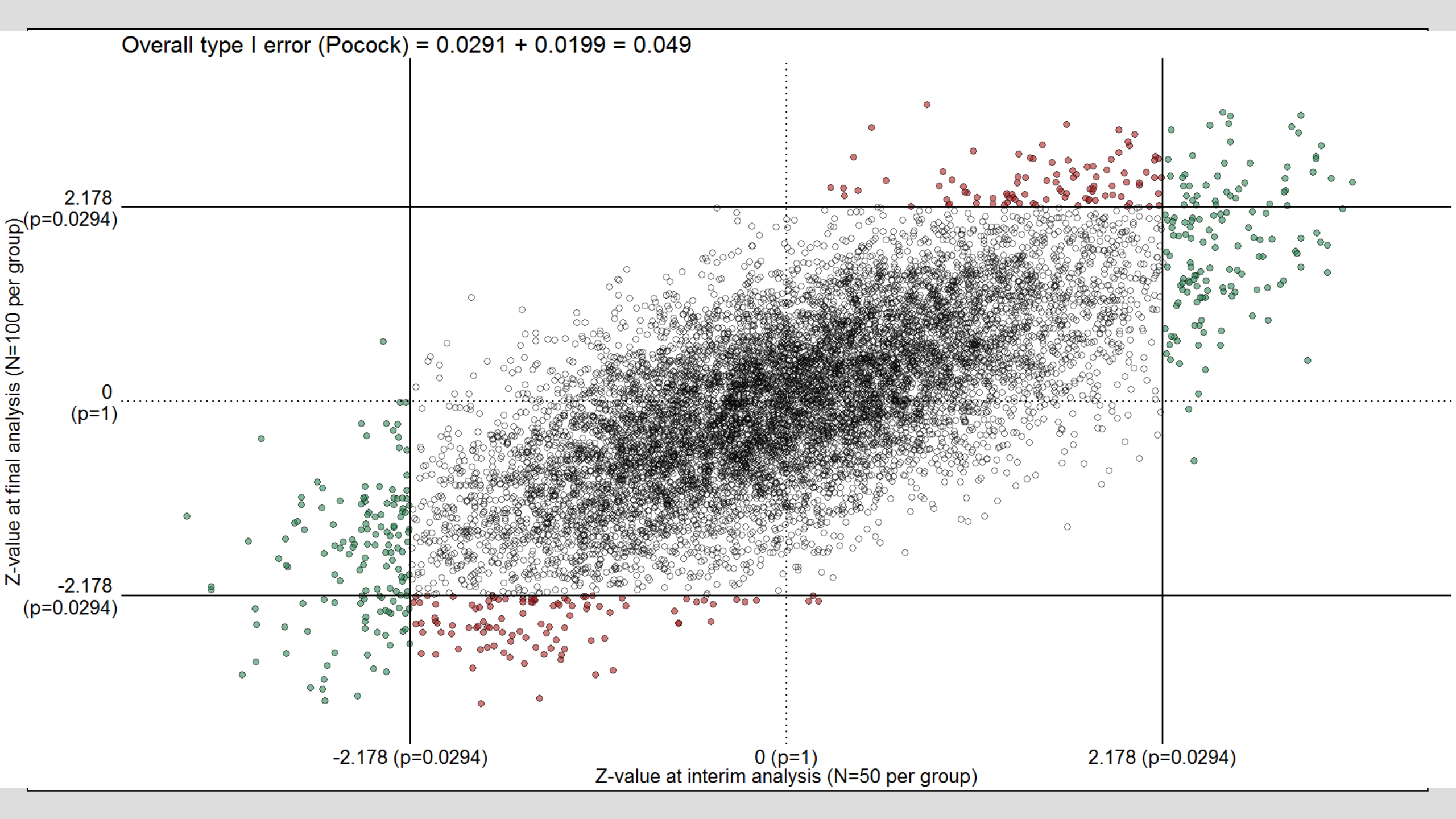

Z-value at final analysis (N=100 per group)
3
2
1
0
-1
-2
-3
-3
-2
-1
0
1
2
3
Z-value at interim analysis (N=50 per group)

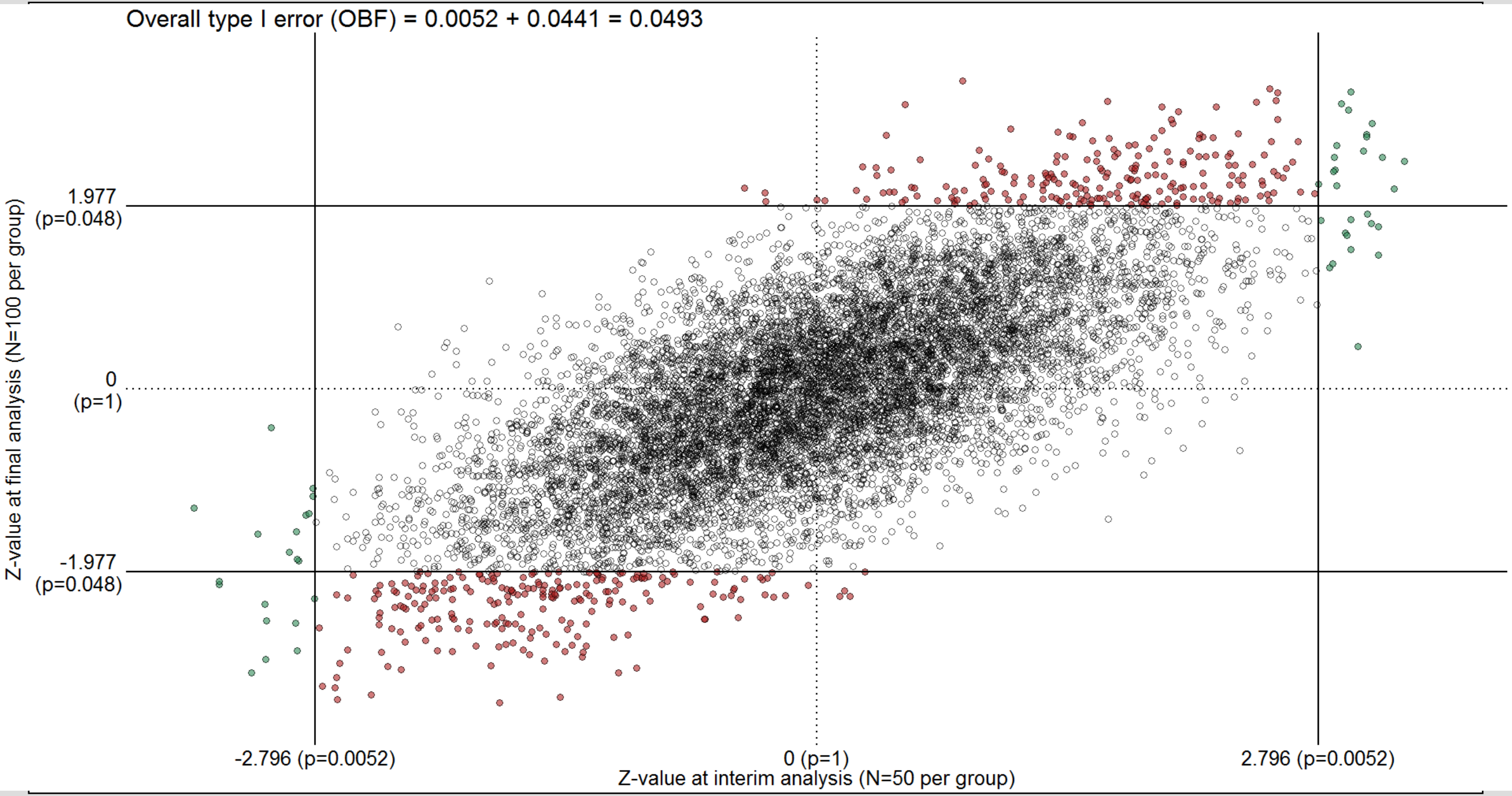

3
2
1
0
-1
-2
-3
Z-value at final analysis (N=100 per group)
-1.96 (p=0.05)
0 (p=1)
1.96 (p=0.05)
Z-value at interim analysis (N=50 per group)


1.96
(p=0.05)
0
(p=1)
-1.96
(p=0.05)
Z-value at final analysis (N=100 per group)
-1.96 (p=0.05)
0 (p=1)
1.96 (p=0.05)
Z-value at interim analysis (N=50 per group)


Overall type I error (No correction) = 0.0481 + 0.0321 = 0.0802
1.96
(p=0.05)
0
(p=1)
-1.96
(p=0.05)
Z-value at final analysis (N=100 per group)
-1.96 (p=0.05)
0 (p=1)
1.96 (p=0.05)
Z-value at interim analysis (N=50 per group)


Overall type I error (Bonferroni) = 0.0245 + 0.0171 = 0.0416
2.241
(p=0.025)
0
(p=1)
-2.241
(p=0.025)
Z-value at final analysis (N=100 per group)
-2.241 (p=0.025)
0 (p=1)
2.241 (p=0.025)
Z-value at interim analysis (N=50 per group)


Overall type I error (Pocock) = 0.0291 + 0.0199 = 0.049
2.178
(p=0.0294)
0
(p=1)
-2.178
(p=0.0294)
Z-value at final analysis (N=100 per group)
-2.178 (p=0.0294)
0 (p=1)
2.178 (p=0.0294)
Z-value at interim analysis (N=50 per group)


Overall type I error (OBF) = 0.0052 + 0.0441 = 0.0493
1.977
(p=0.048)
0
(p=1)
-1.977
(p=0.048)
Z-value at final analysis (N=100 per group)
-2.796 (p=0.0052)
0 (p=1)
2.796 (p=0.0052)
Z-value at interim analysis (N=50 per group)

Wang and Tsiatis power family (1987)

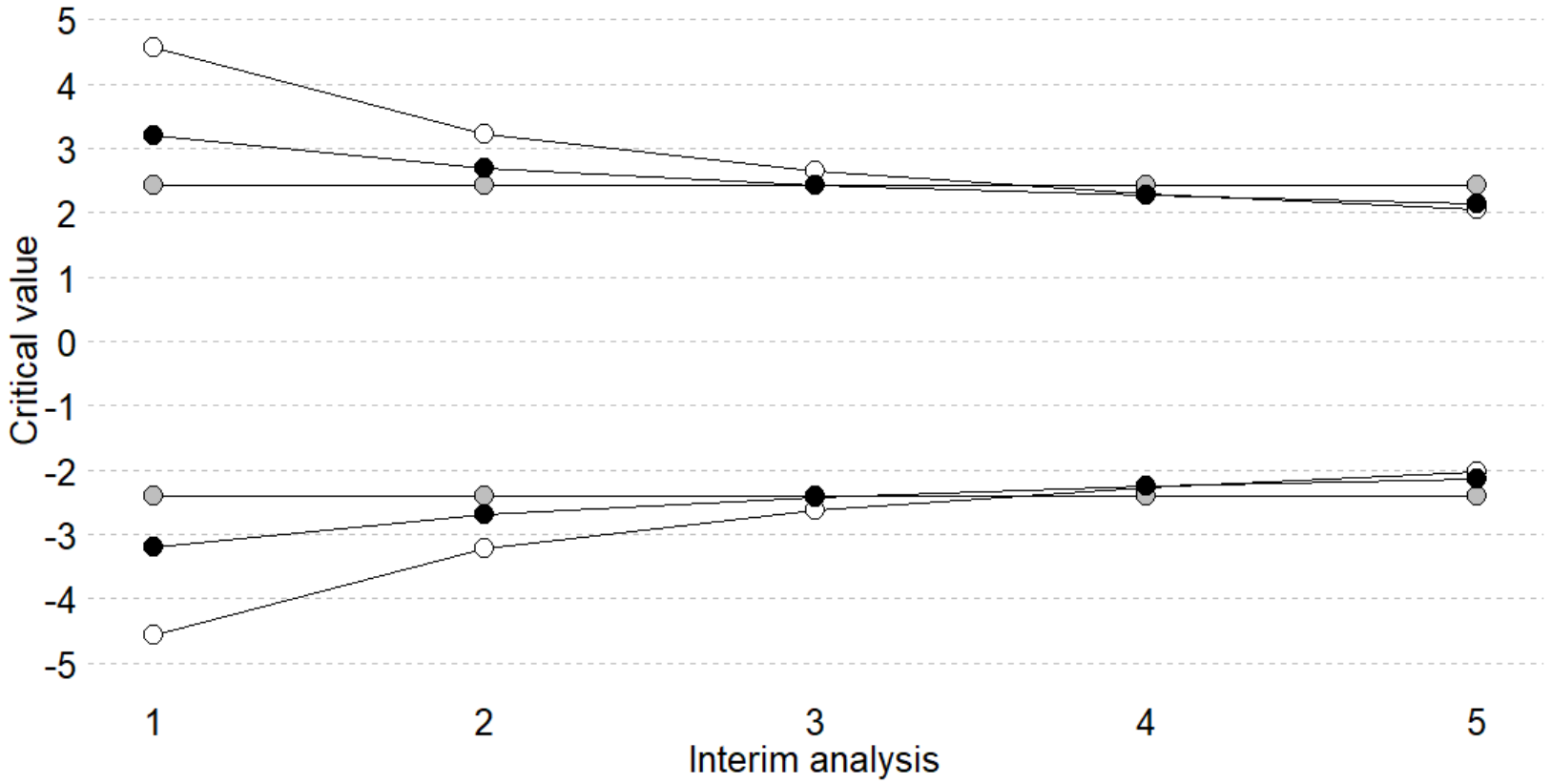
- Class of boundaries indexed by a power parameter Δ

$$c_i = c_{WT}(K, \alpha, \Delta) i^{\Delta - 0.5}$$

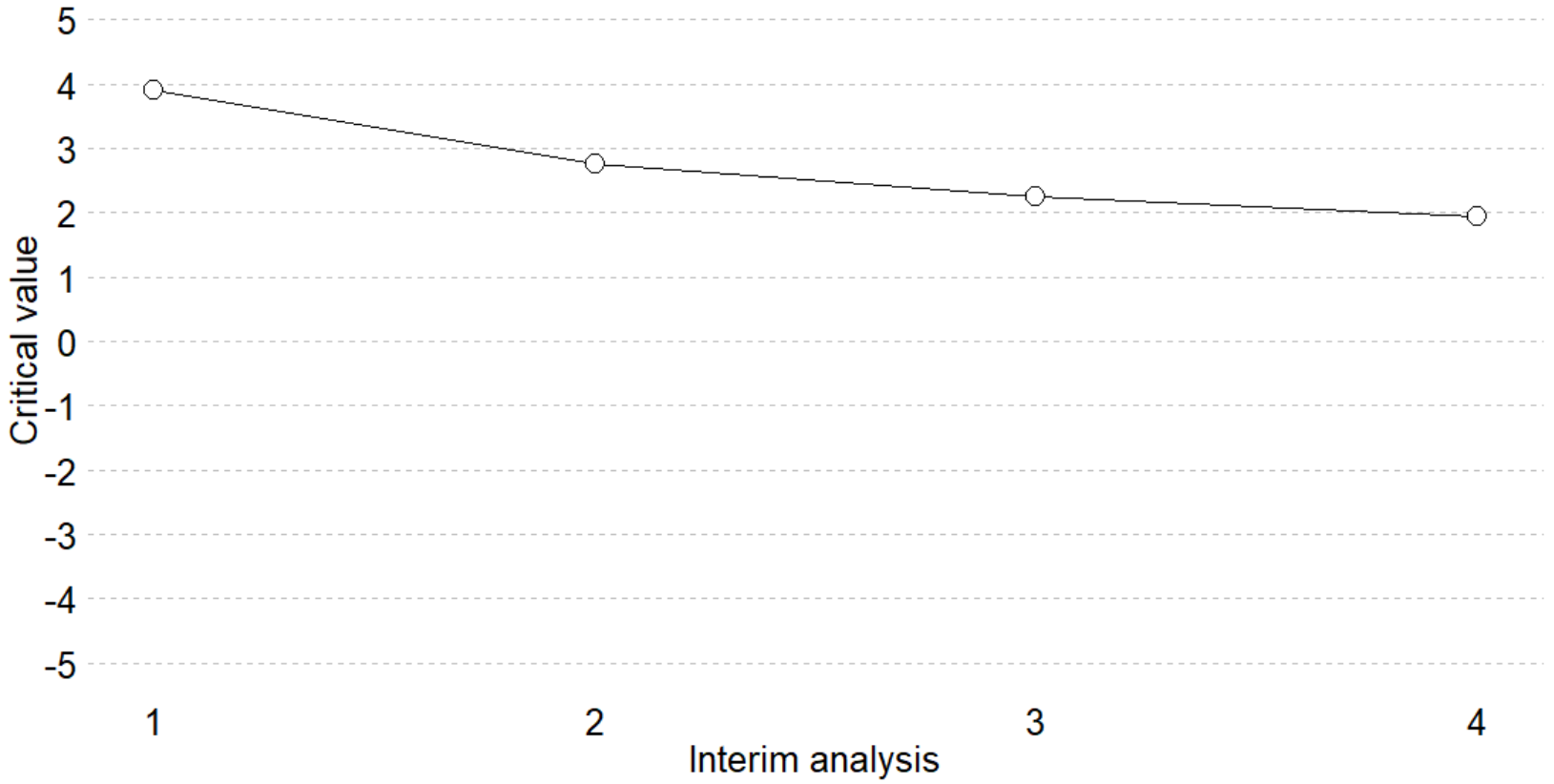
- $\Delta = 0$ → O'brien and Fleming. $\Delta = 0.5$ → Pocock

- Can use Δ to minimize the ASN for determining maximum sample size

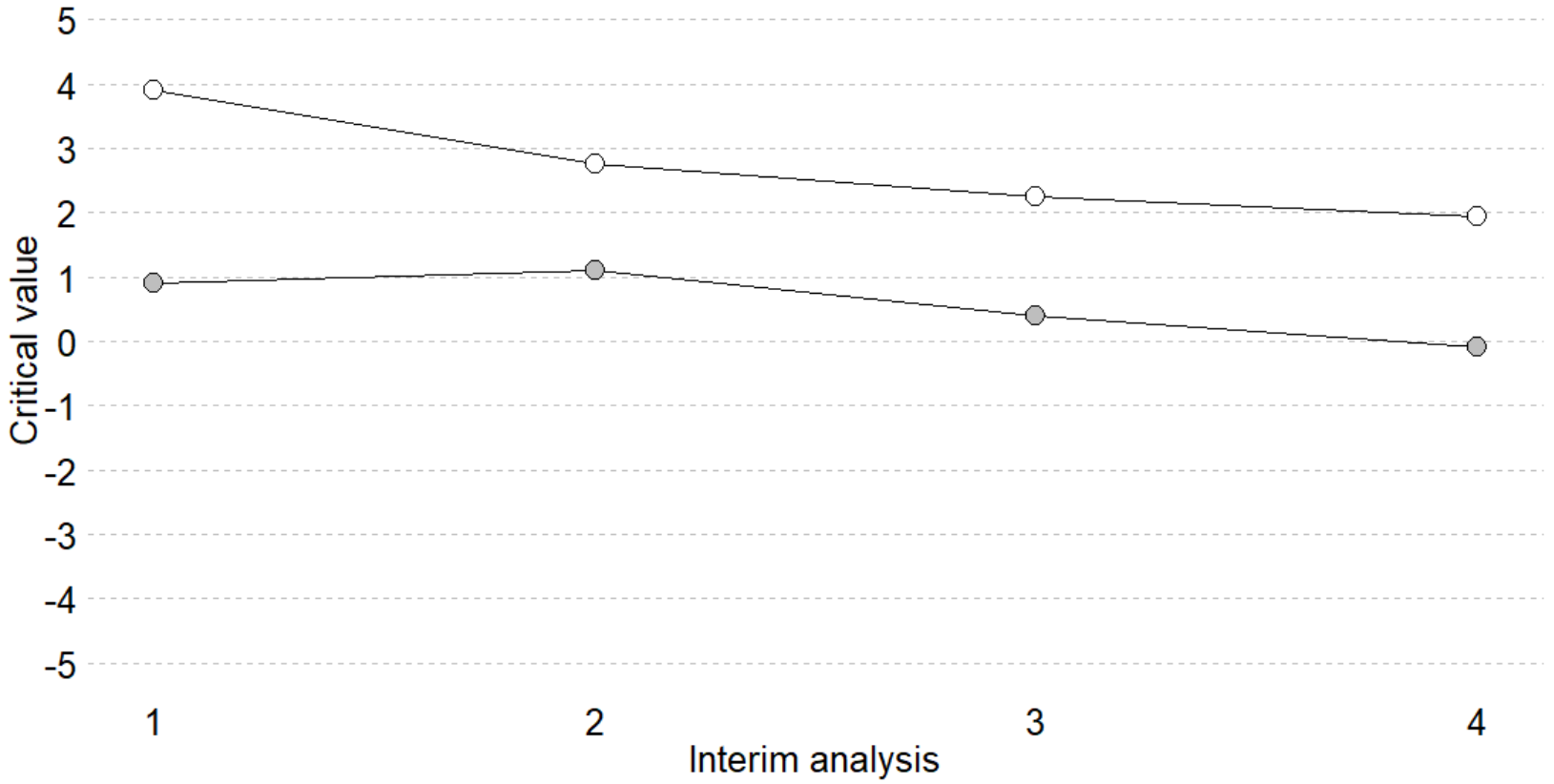
Stopping boundaries (WT : Δ=0.25)



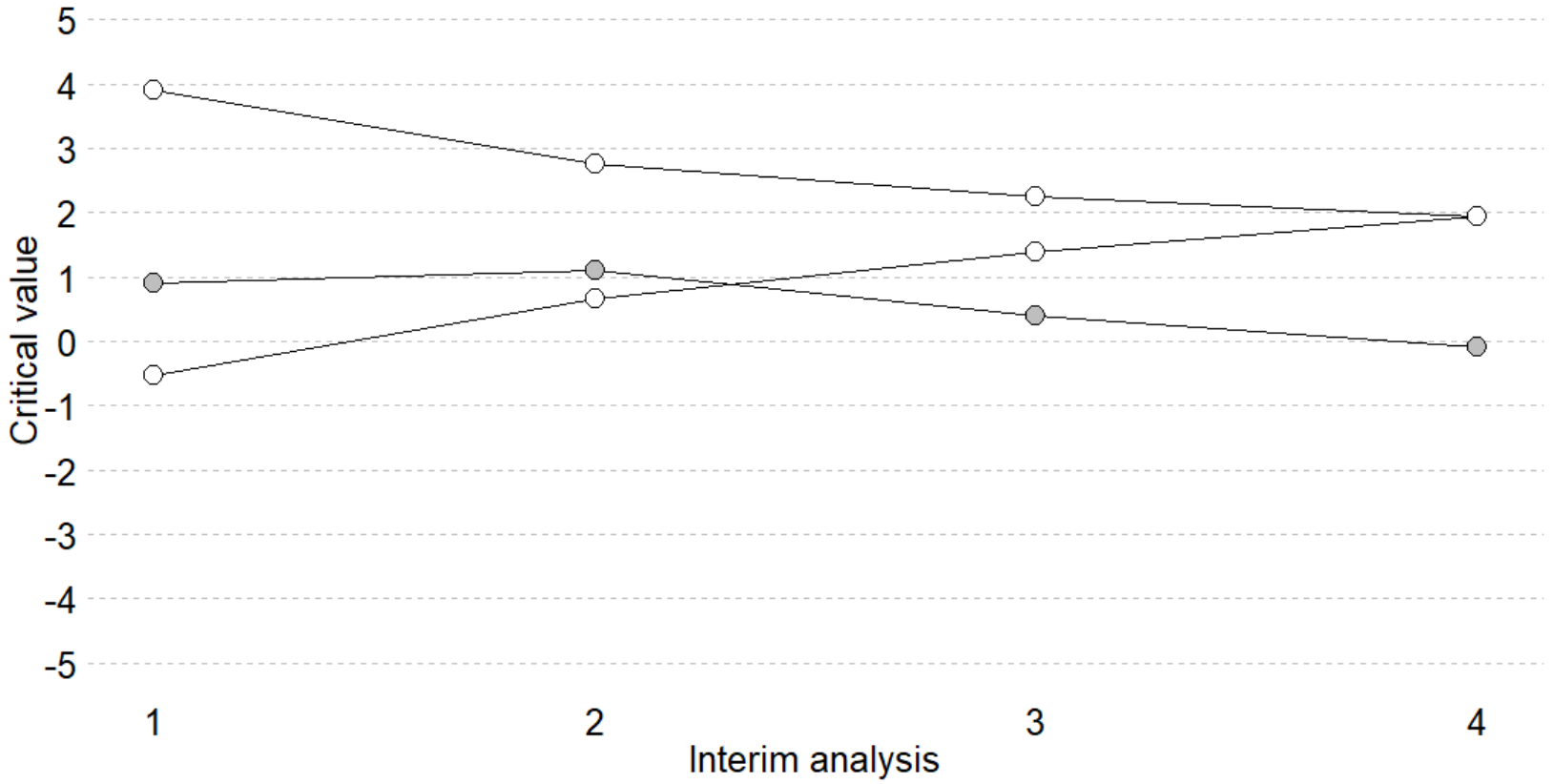
One-sided test and futility stopping



One-sided test and futility stopping



One-sided test and futility stopping



Binding and non-binding futility boundaries

- Analoglously to efficacy boundaries, futility boundaries attempt to control the type II error
- Type II error is under H_a, which assume a treatment effect Δ
- When adding futility boundaries, the critical efficacy boundaries can be slightly relaxed
- In this case, the futility boundaries are *binding* → stopping is mandatory when the boundary is crossed to preserve type I error
- Recommend to use *non-binding* boundaries → Futility boundaries serve as guidelines

Conditional power

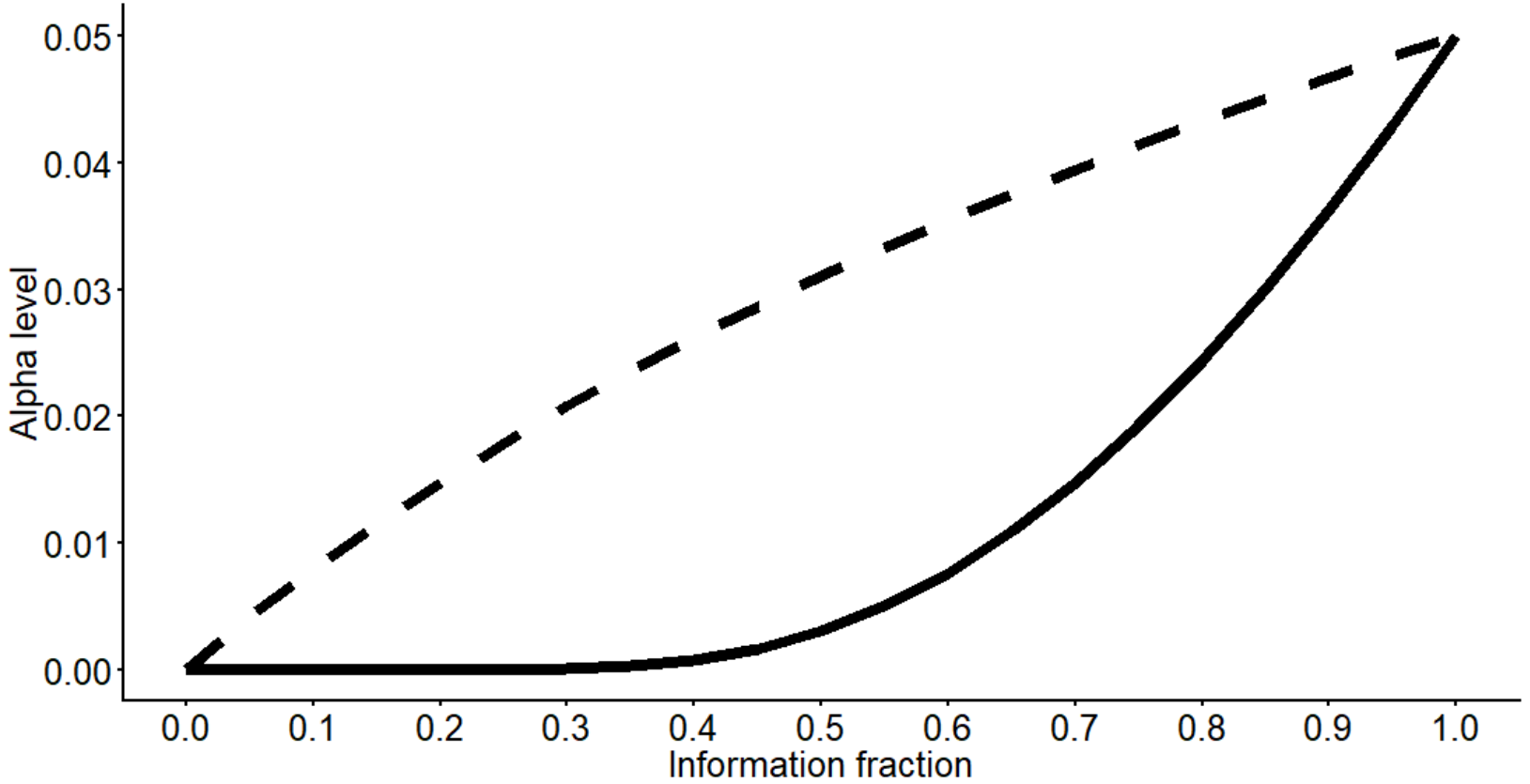
- Given the interim results, what is the chance of success at the final analysis?
- Conditional power (CP) allows to quantify this probability
- Continue the trial only if CP is high enough, e.g. CP = 0.8 or CP = 0.9

- Also possible to increase the sample size if CP not high enough
- Mehta and Pocock (2011) proposed the *promising zone* approach

α-spending function approach

- Lan & DeMets (1994)
- Allow flexibility in the number of interim analyses to be conducted and at what times
- α–spending function $\alpha(t_k)$ is an increasing function depending on t_k satisfying $\alpha(0) = 0$ and $\alpha(1) = \alpha$
- $t_k = n_k/N_{max}$ = information rate
- α considered as a budgeted quantity to spend

Pocock and OBF spending functions



Procedure α is spent

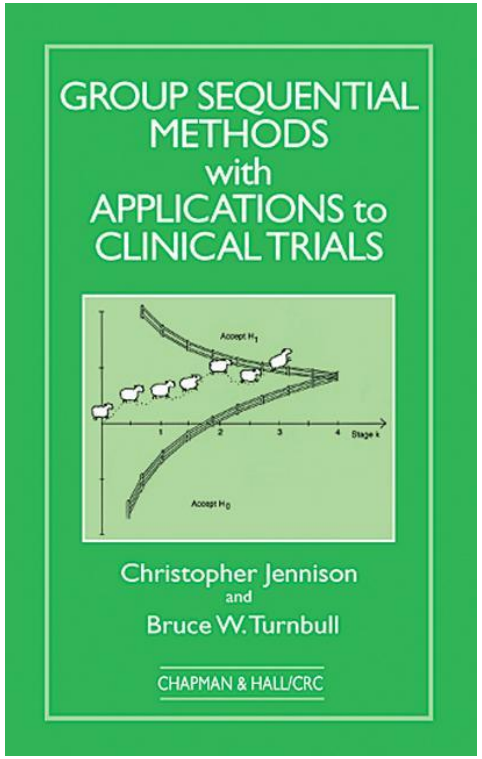
- $P_1 = P_{H_0}(|Z_1| \geq u_1) = \ \alpha(t_1)$
- $P_2 = P_{H_0}(|Z_1| < u_1, |Z_2| \geq u_2) = \ \alpha(t_2) - \alpha(t_1)$
- …
- $P_k = \alpha(t_k) - \alpha(t_{k-1})$

- $P_1 + \cdots + P_K = \alpha$

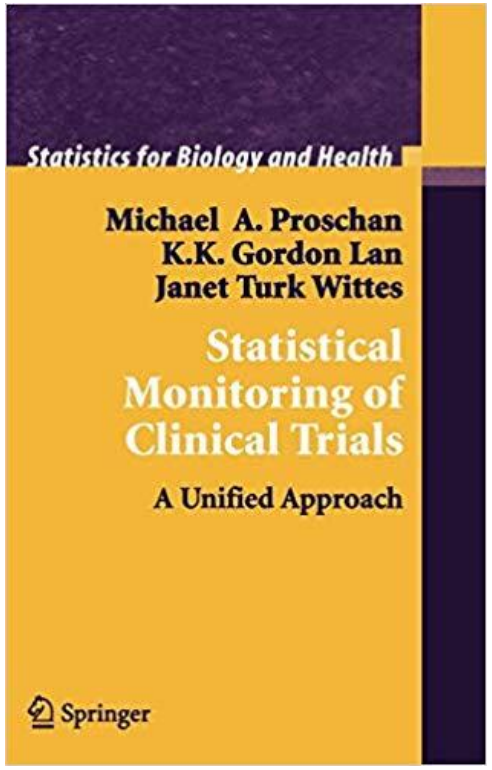
- Z_k depends only on the information rates t_1, … t_k,not on the unobserved ones $t_{k+1}, \ldots t_K$

References

(1999)



(2006)



(2016)