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EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

Early stopping, allocation ratios and power:

How to tailor design options for a platform trial in Major Depressive Disorder

ADMTP 2023
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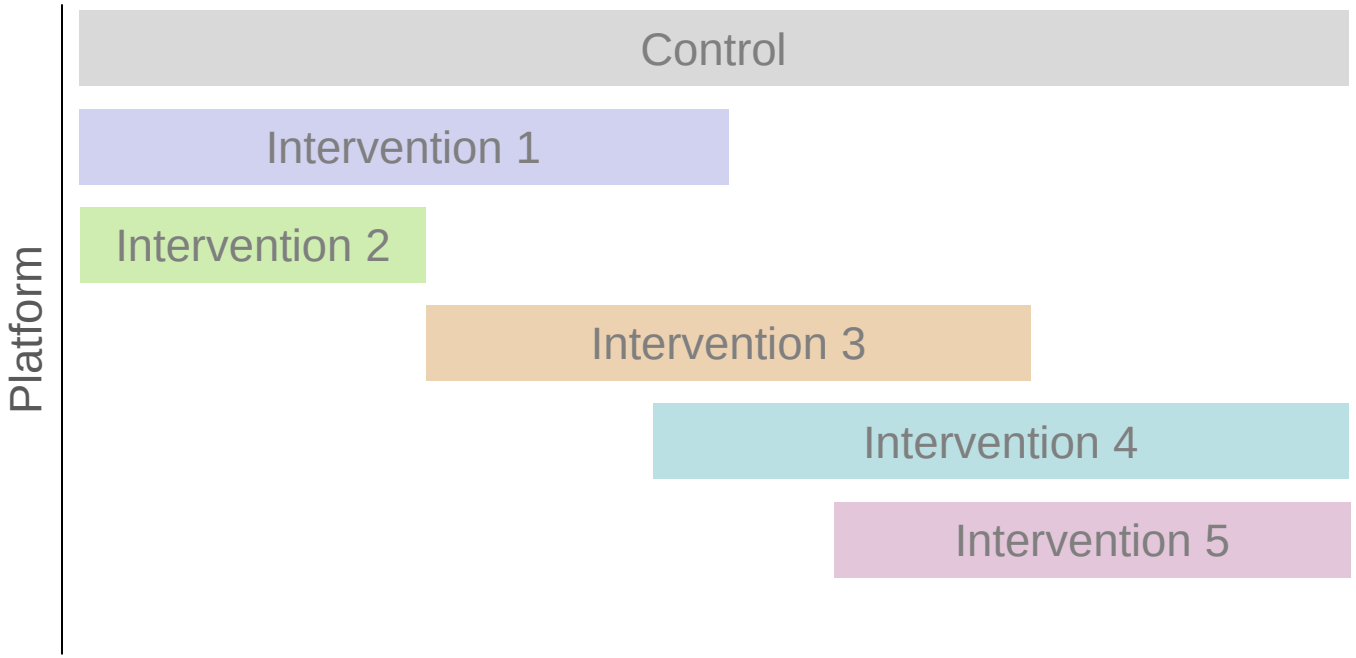
"This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 853966. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and CHILDREN'S TUMOR FOUNDATION, GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT NON PROFIT ORGANISATION, SPRINGWORKS THERAPEUTICS INC". *This presentation reflects the author's view. Neither IMI nor the European Union, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained.*

Platform Trials

- Simultaneous and sequential evaluation of multiple interventions in one indication against a common control (possibly divided by specific disease sub-types)
- Treatments joining or leaving the trial over time



Major Depressive Disorder (MDD)

- **Affects 5-6% of the population worldwide at any given time, with a 1 in 6 lifetime prevalence *(Otte et al, Nature Reviews Disease Primers 2016)***
- O**ne of the leading causes of disability worldwide *(WHO, 2018)***
- Difficult to treat: about 50% of patients do not benefit sufficiently from first treatment (Partially Responsive Depression, **PRD**) and the majority of these also do not benefit from second-line treatment (Treatment-Resistant Depression, **TRD**)
  (Rush et al, American Journal Psychiatry 2006)
- Very few new drugs (especially with new mechanisms of action) have been developed in the past decades

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We want to design an efficient platform trial especially tailored for MDD

Basics Elements for the Study

Inclusion	patients with treatment resistant depression (**TRD**)
Endpoint	Primary: **MADRS Clinician-based Rating scale** at week 6 compared to baseline
Treatment Duration	**6 weeks** (+ 4 weeks run-in period)
Treatments and Comparators	**Augmentation (add on)** to existing antidepressant, with placebo as the comparison
Recruitment speed	About 1 patient per side and month (here: mean 7 per week)

Design Choices and Assumptions

Platform duration	Last compound added at the latest at Month 60 (recruiting until all arms finished)
Treatment arms	Max. 6 concurrent treatment arms at any time
Controls	Concurrent controls only
Effect sizes	d=0.00 vs d=0.2 vs d=0.35 vs d=0.50
Sample size	Range of possible samples sizes (N=40 to N=120) per experimental arm
Final analysis	Analysis of covariance with baseline value as a covariate (**rho = 0.214)** and without adjustment for multiplicity
Decision rule	One-sided p<0.05 to claim success at final analysis
Allocation ratio	• 1:…:1 • 1:1:…: k , where k is the current number of experimental arms • 1:1:…:$\sqrt{k}$ • 1:1:…:$\sqrt{k}$, ***but*** at least 35% placebo (i.e. Placebo allocation range 35-50%)
Interim analysis	Interim analysis for futility (after 50% randomized) ; p<α_0 to continue to second stage

Operating Characteristics

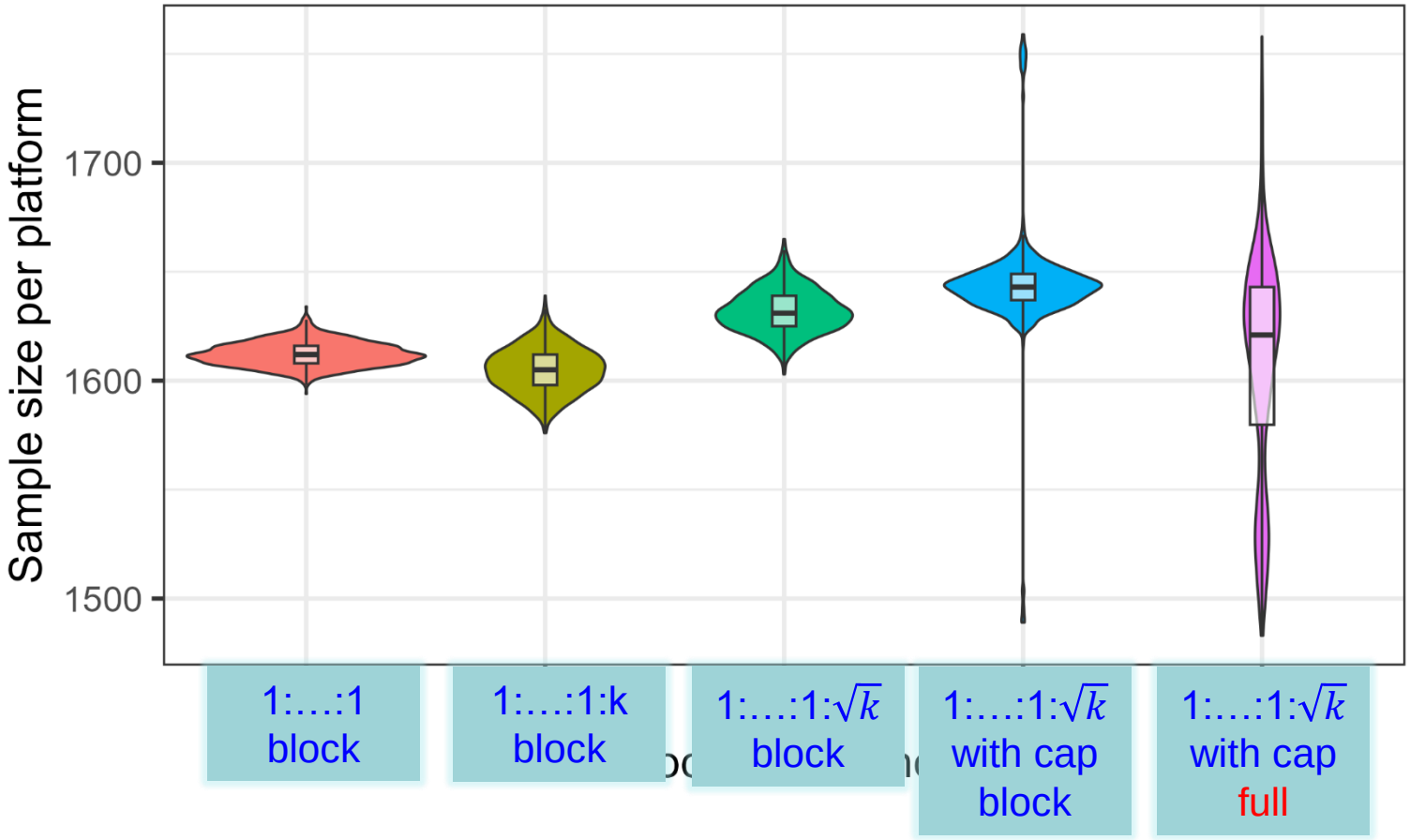
- Sample size of the platform
- Number of treatment arms
- Duration of arms
- Size of concurrent control group
- Rate of decisions made

Reducing Parameter Space for Design and Assumptions

- New treatments can enter every month (defined as 4 weeks)
- Only allow them to enter if 20% of the sample size can be recruited before month 60 (taking into account number of arms concurrently open)
- Number of concurrent arms maximized
- Check if recruitment is finished every week

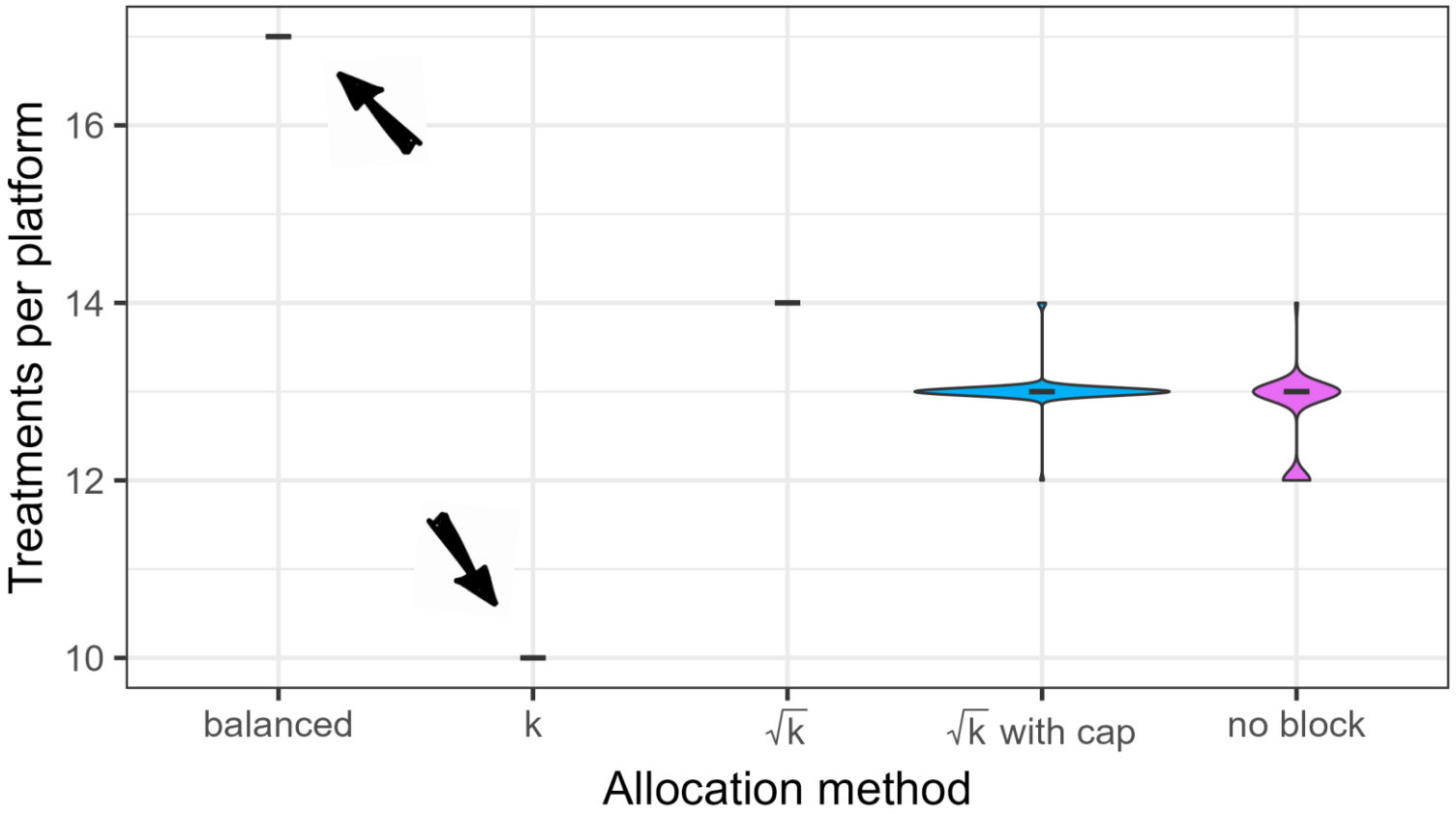
Selection of Allocation Method: Sample Sizes

- Median Sample size between 1605 and 1645



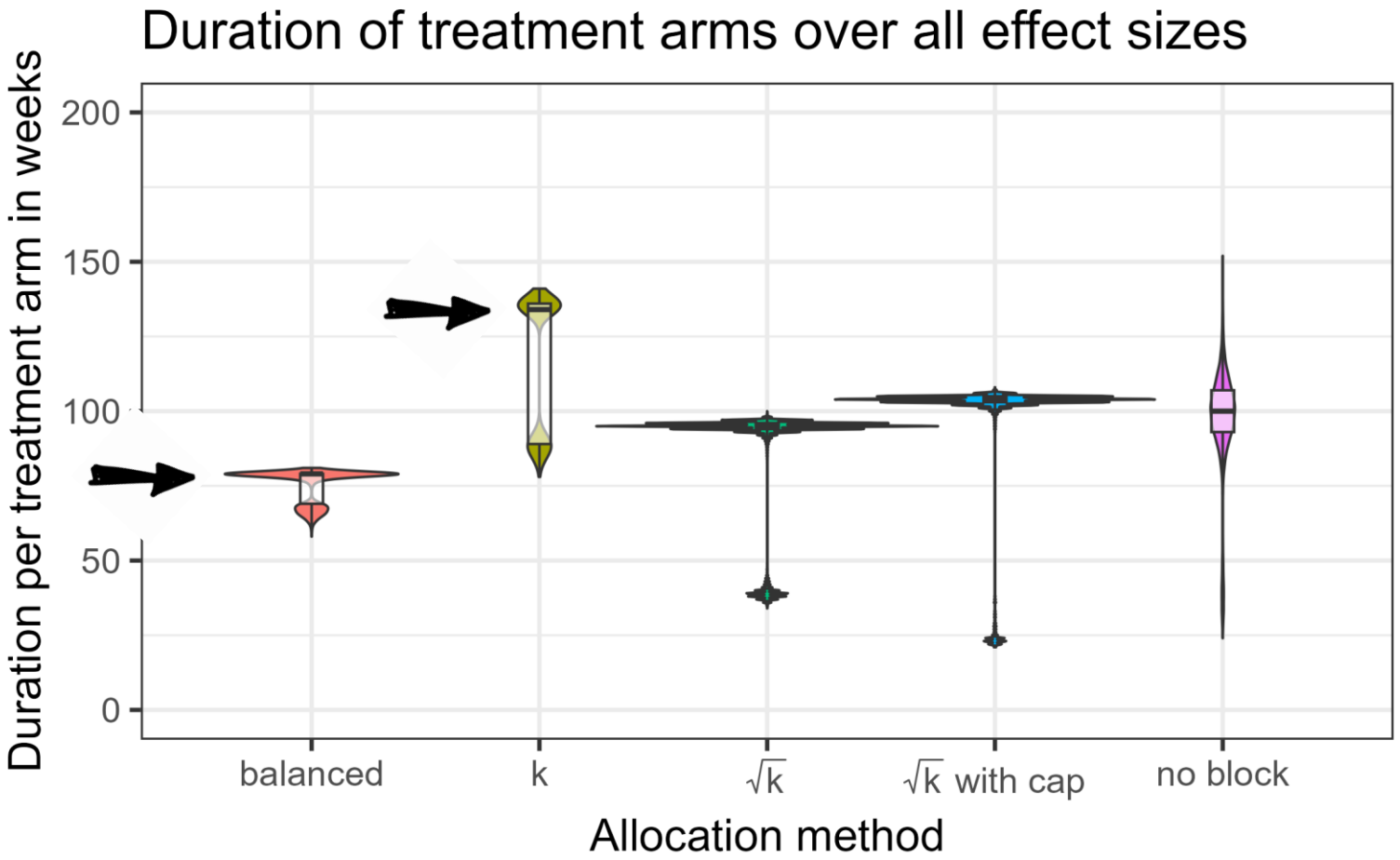
Allocation Method: Arms

- Varying number of arms (10 to 17) depending on allocation method



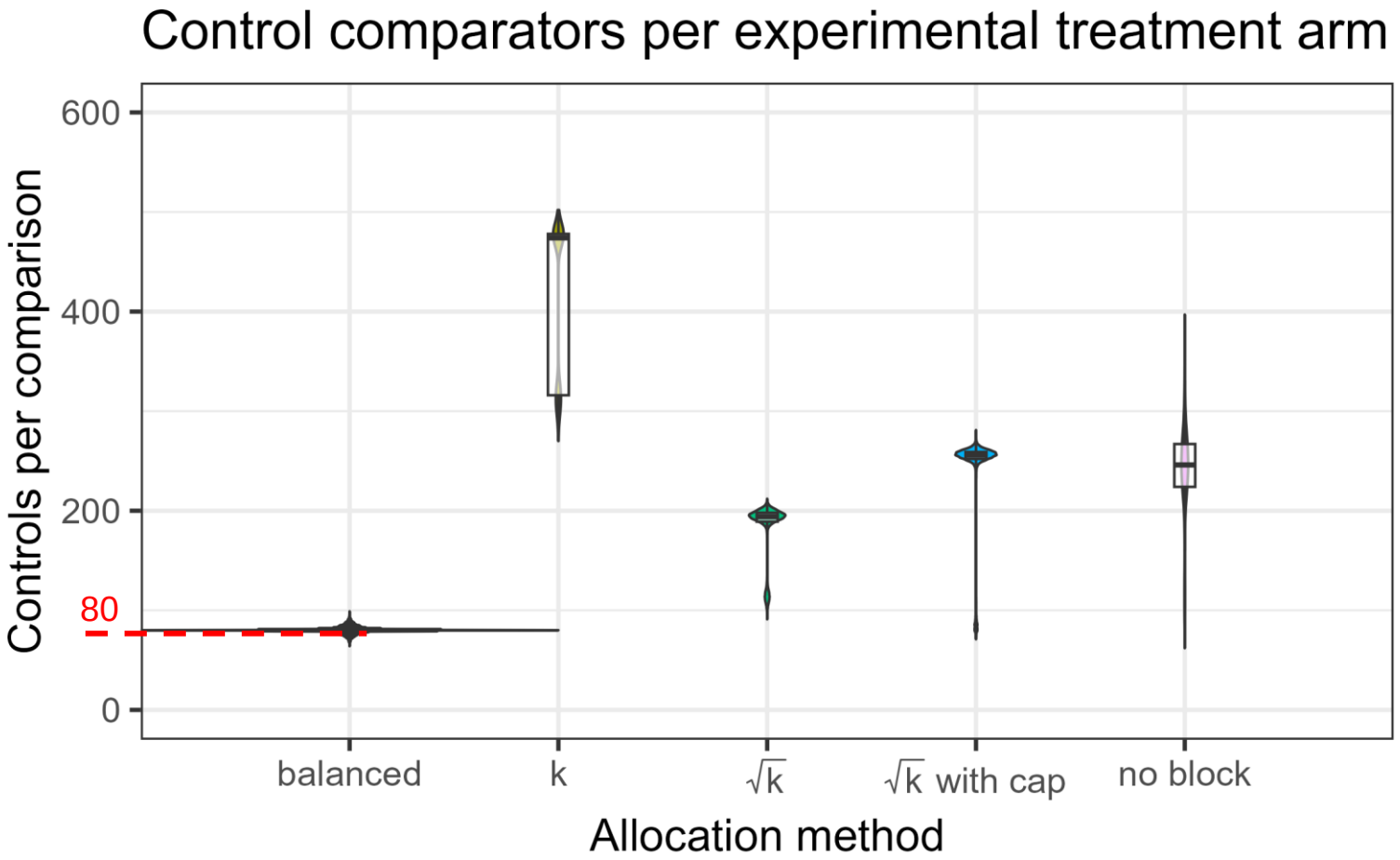
Allocation Method: Duration

- Median duration longest for 1:…:1:k and shortest for 1:…:1

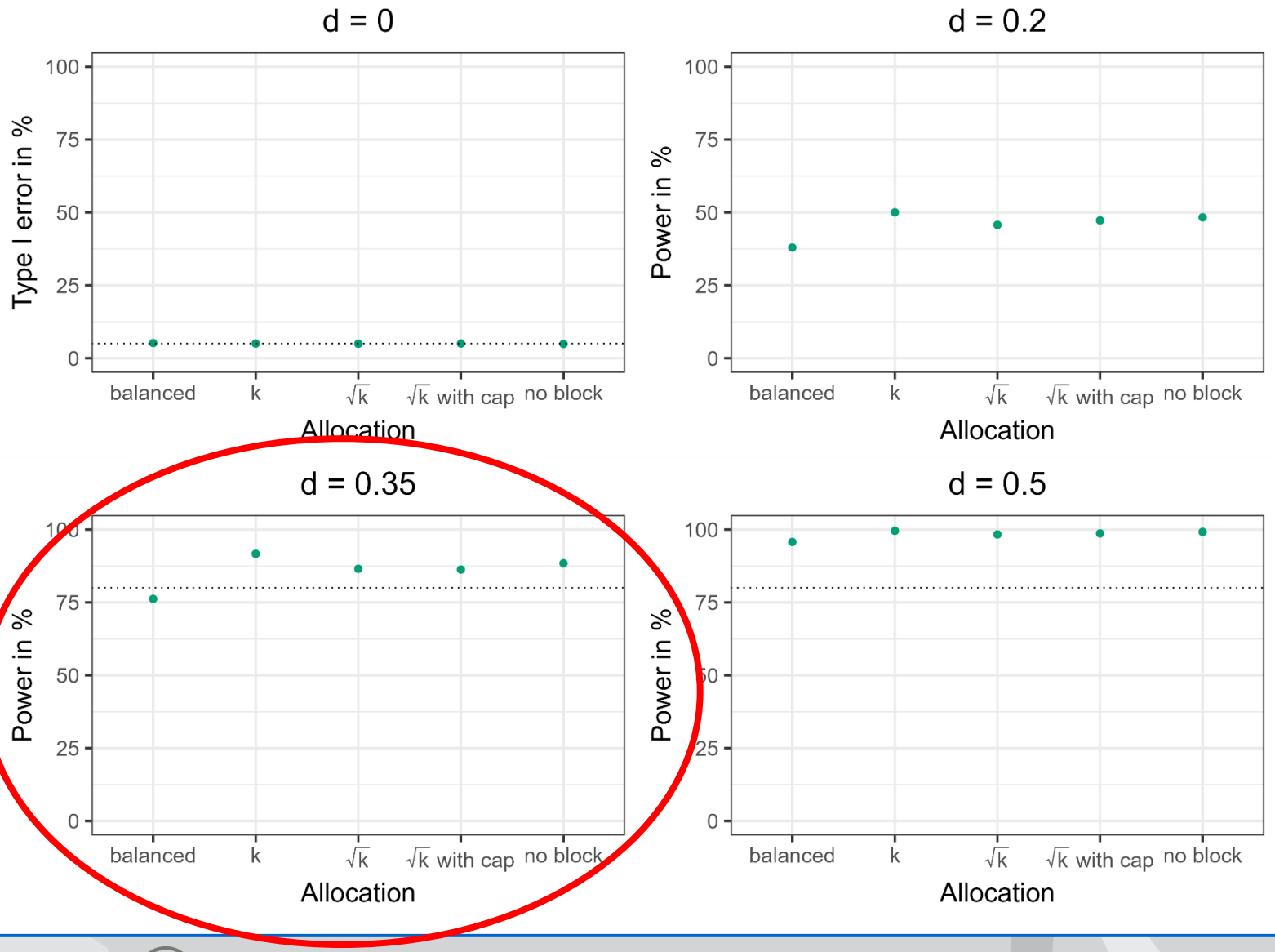


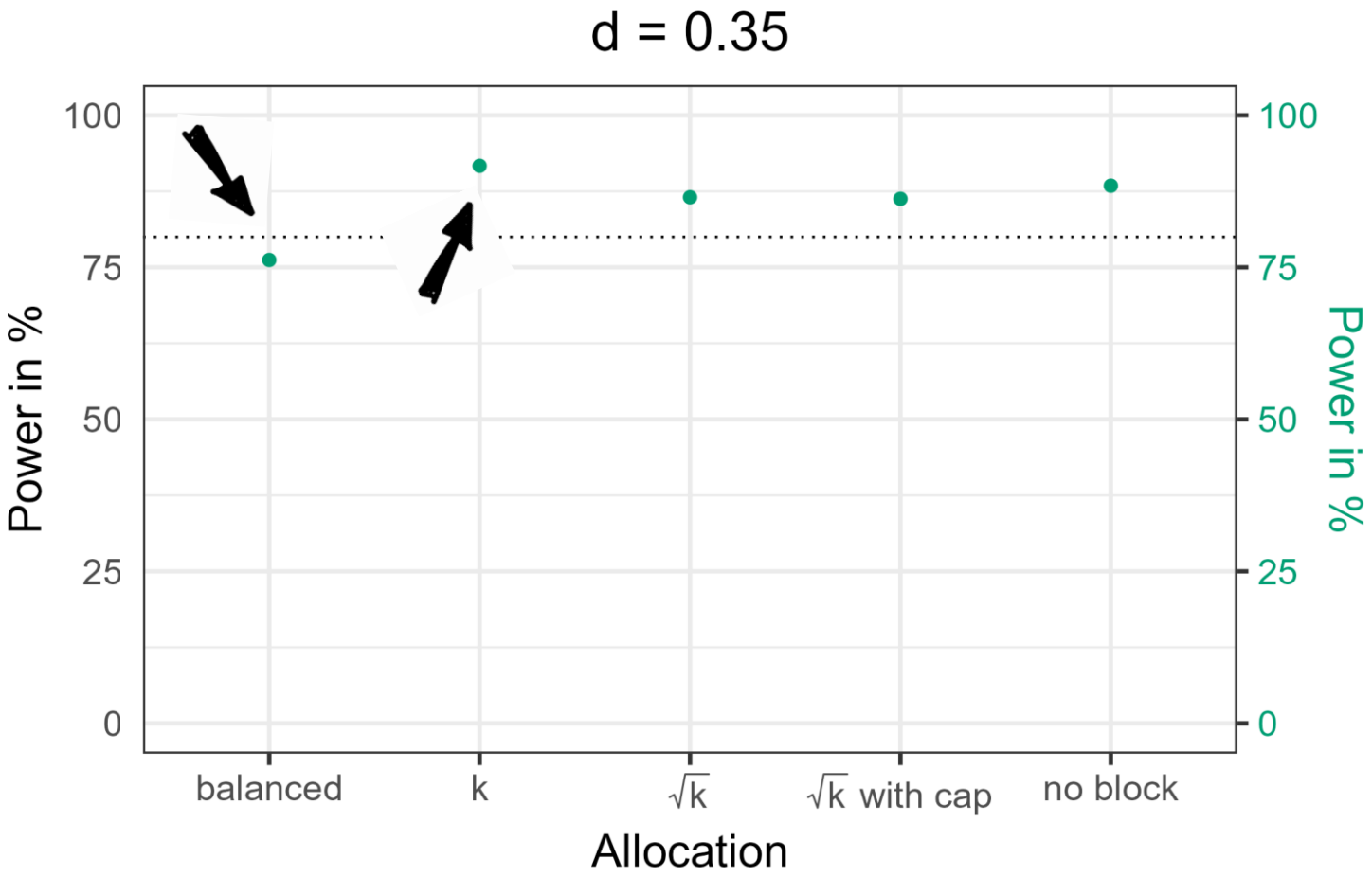
Allocation Method: Control Comparators

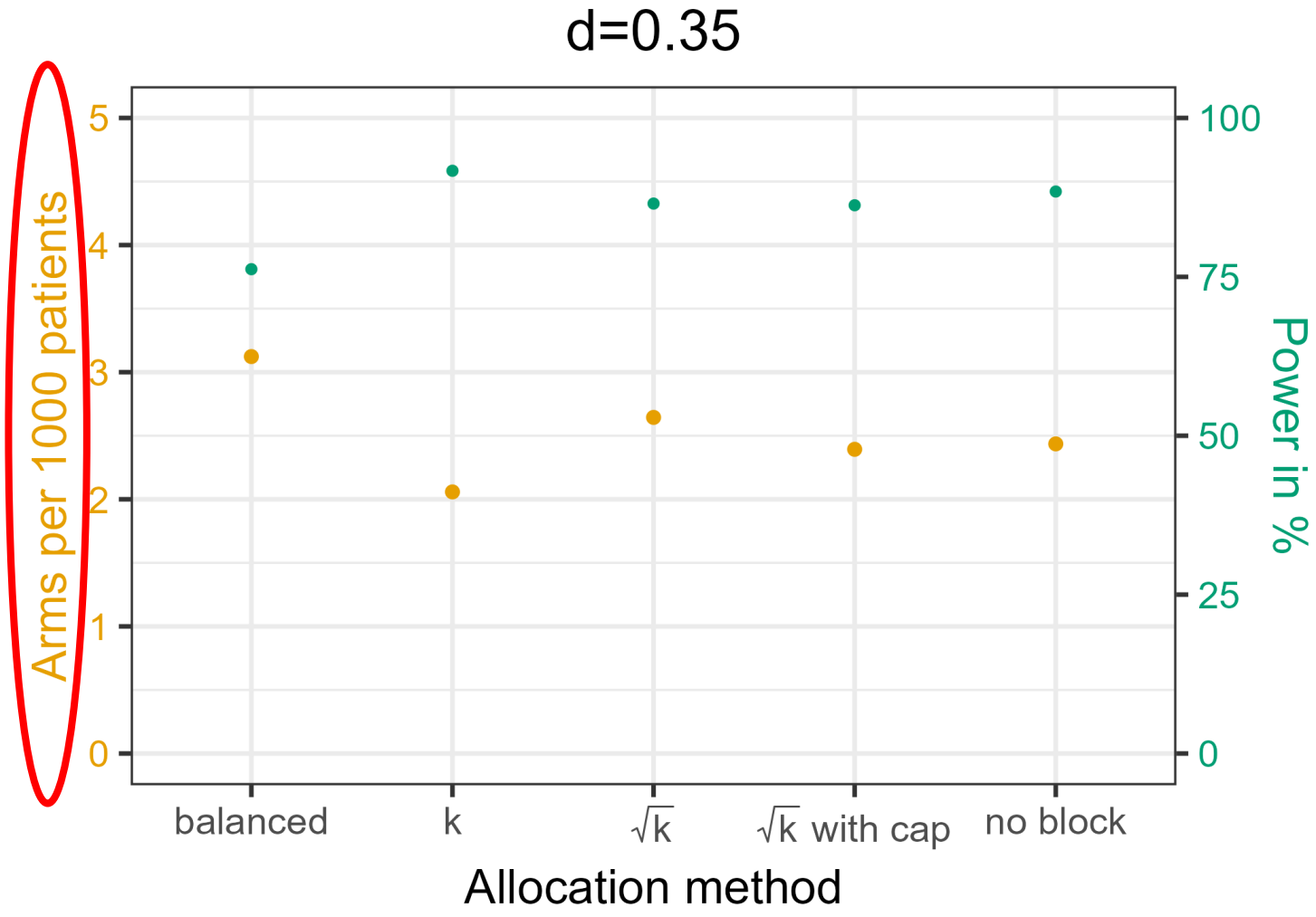
- Longer duration due to larger concurrent control groups



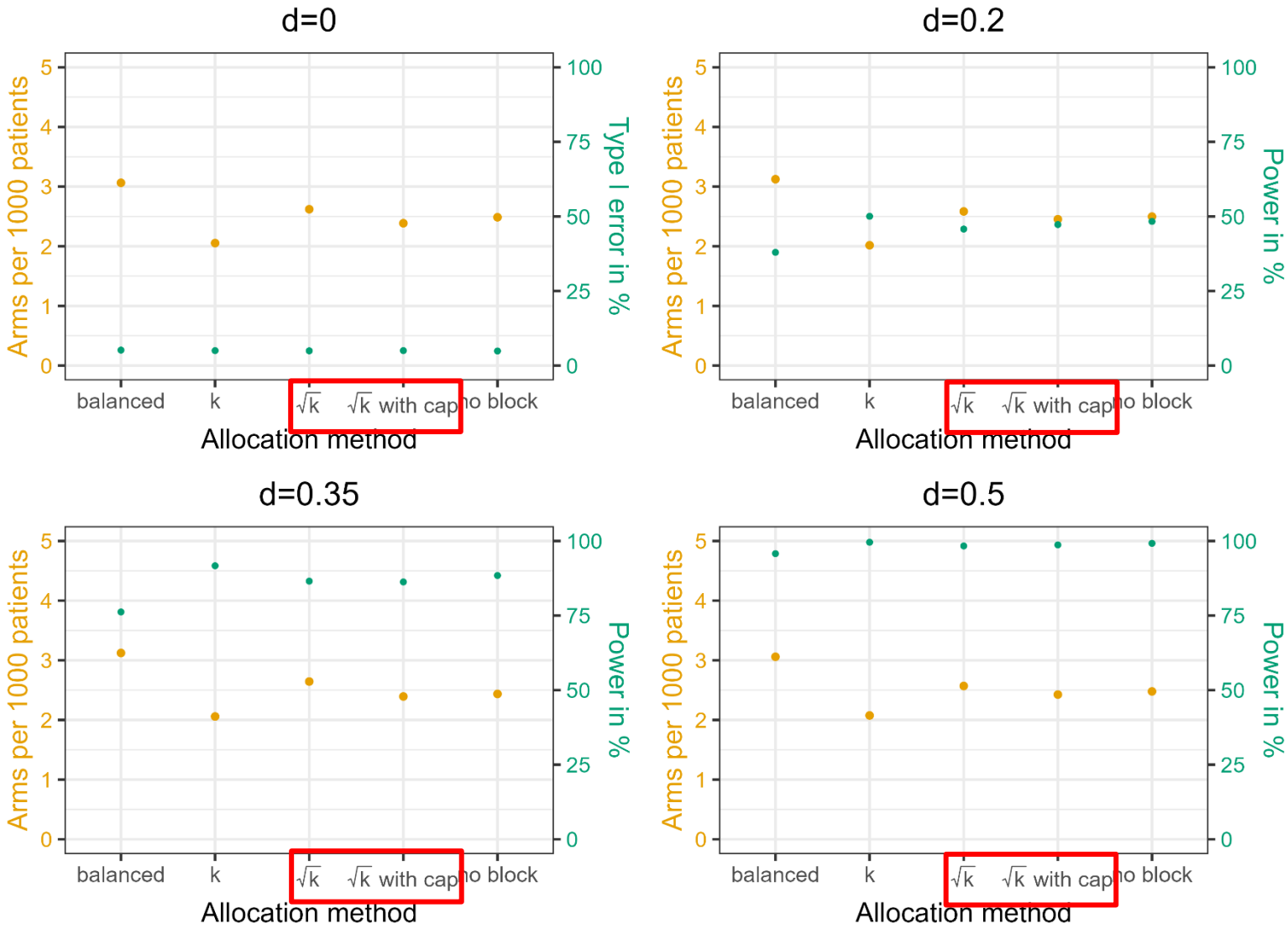
Allocation Method: Power




d = 0.35
100
75
50
25
0
Power in %
balanced
k
√k
√k with cap
no block
Allocation


d=0.35
Arms per 1000 patients
0
1
2
3
4
5
Power in %
0
25
50
75
100
balanced
k
√k
√k with cap
no block
Allocation method

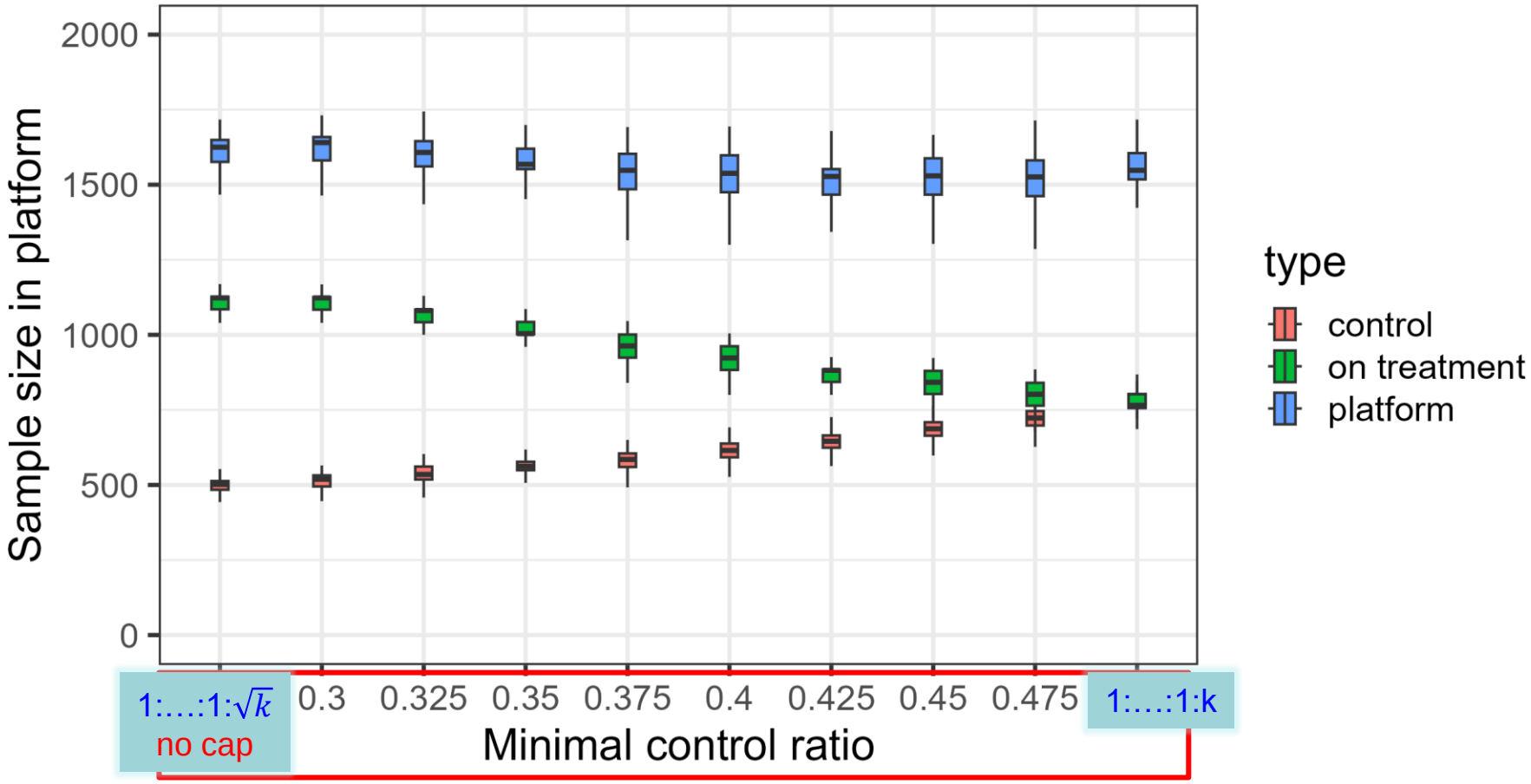
Allocation Method: OCs for Success



How to select the minimal allocation ratio to control?

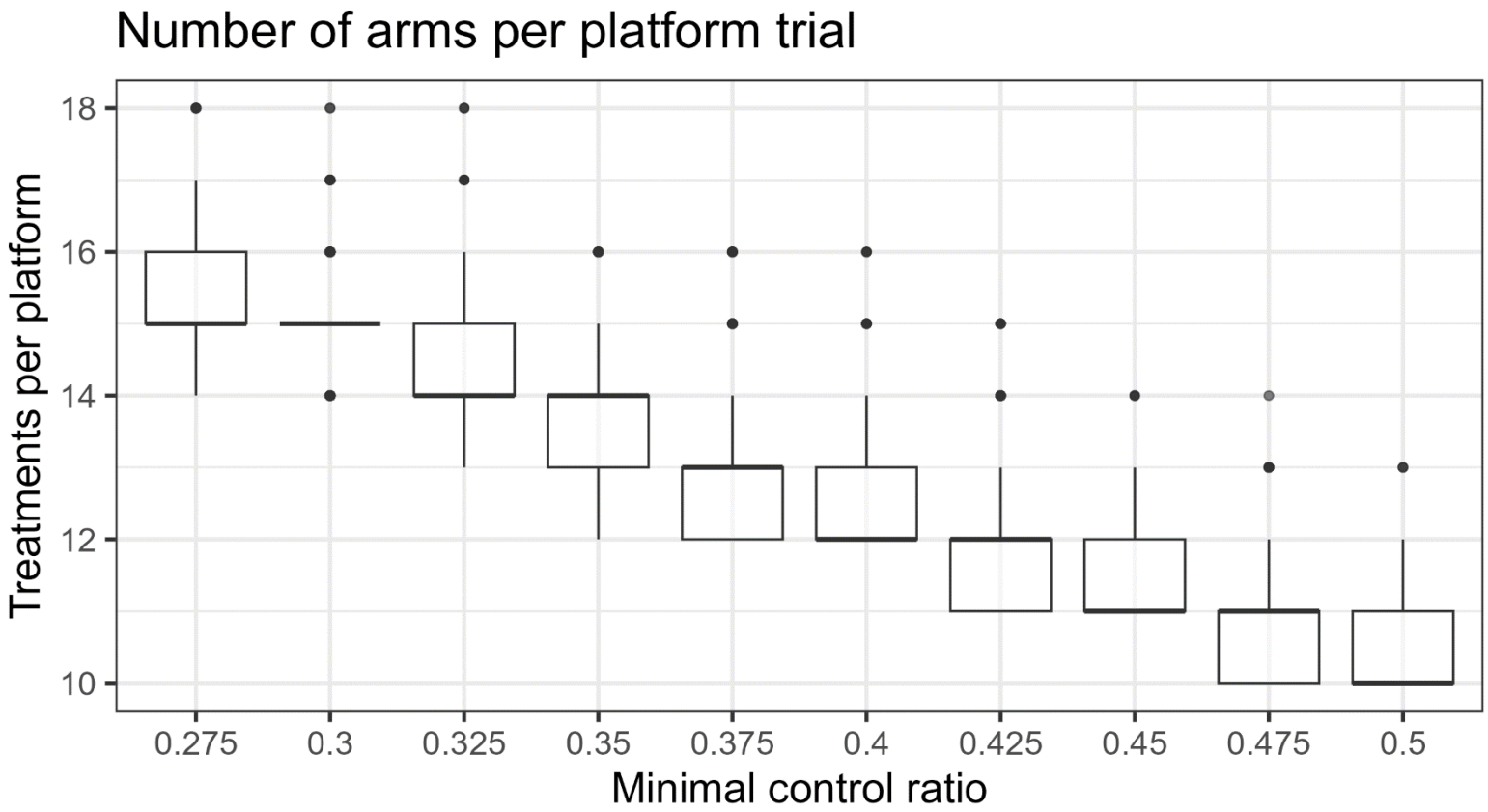
Selecting the Minimal Control Ratio: Sample Sizes

- Higher minimal control ratio leads to fewer patients on treatment



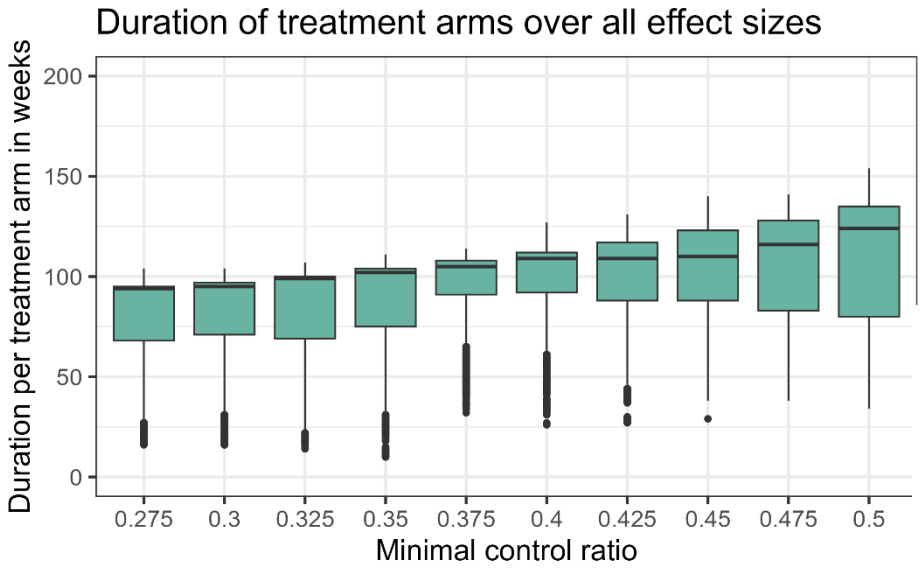
Minimal Control Ratio: Arms

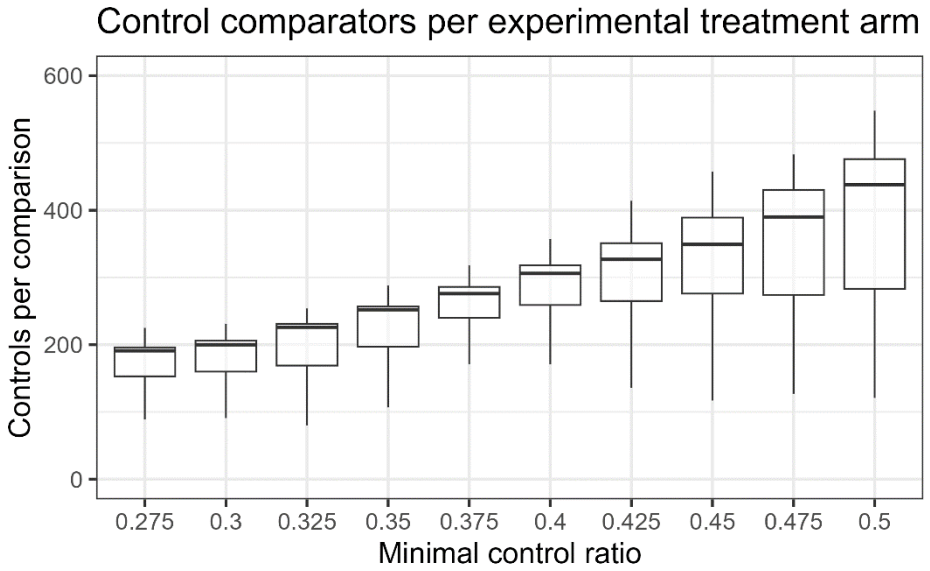
- Fewer arms can be tested with higher minimal control ratio



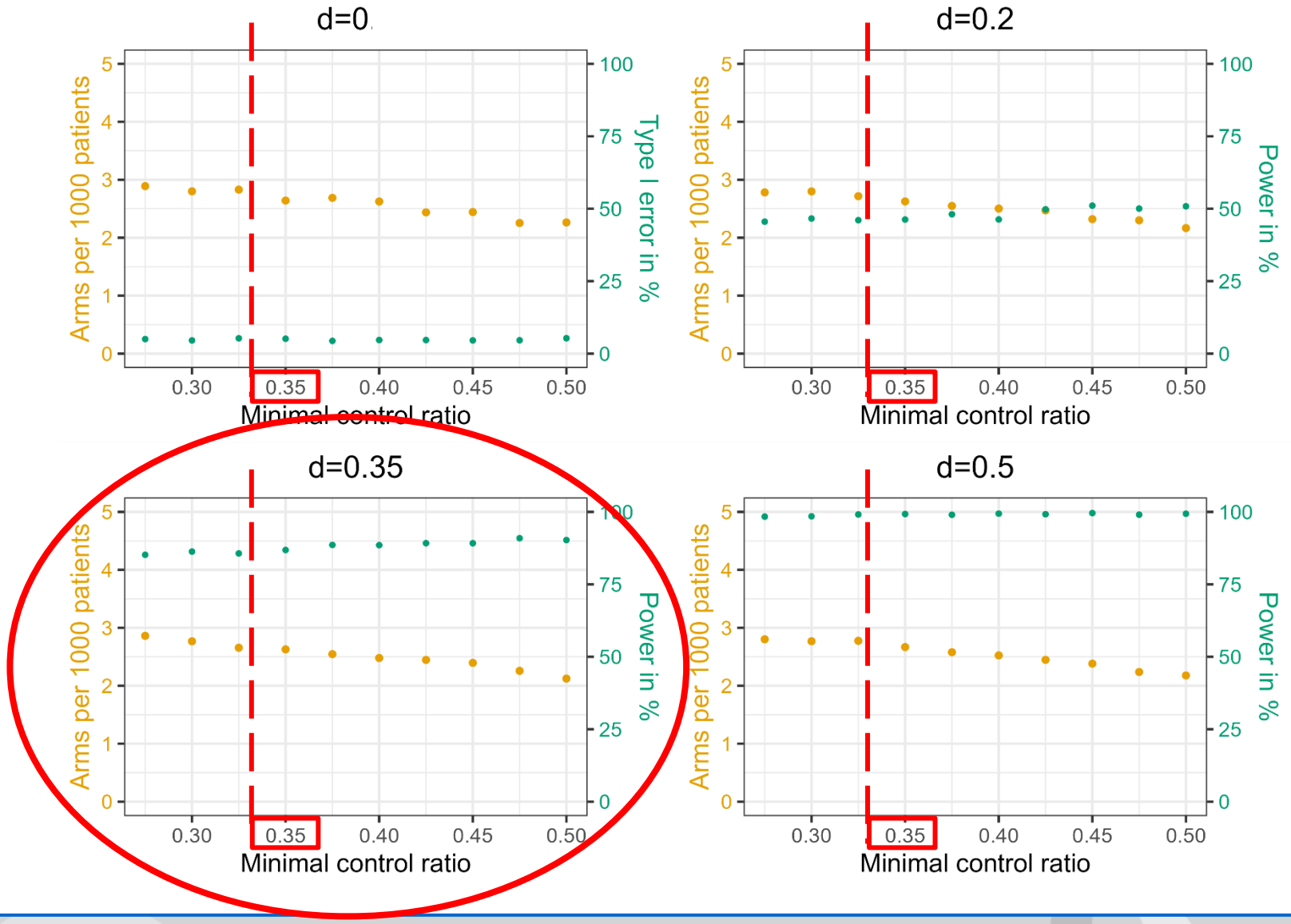
Minimal Control Ratio: Duration and Control Comparators

- Higher minimal control ratio leads to longer duration per treatment arm and larger concurrent control groups





Minimal Control Ratio: OCs for Success



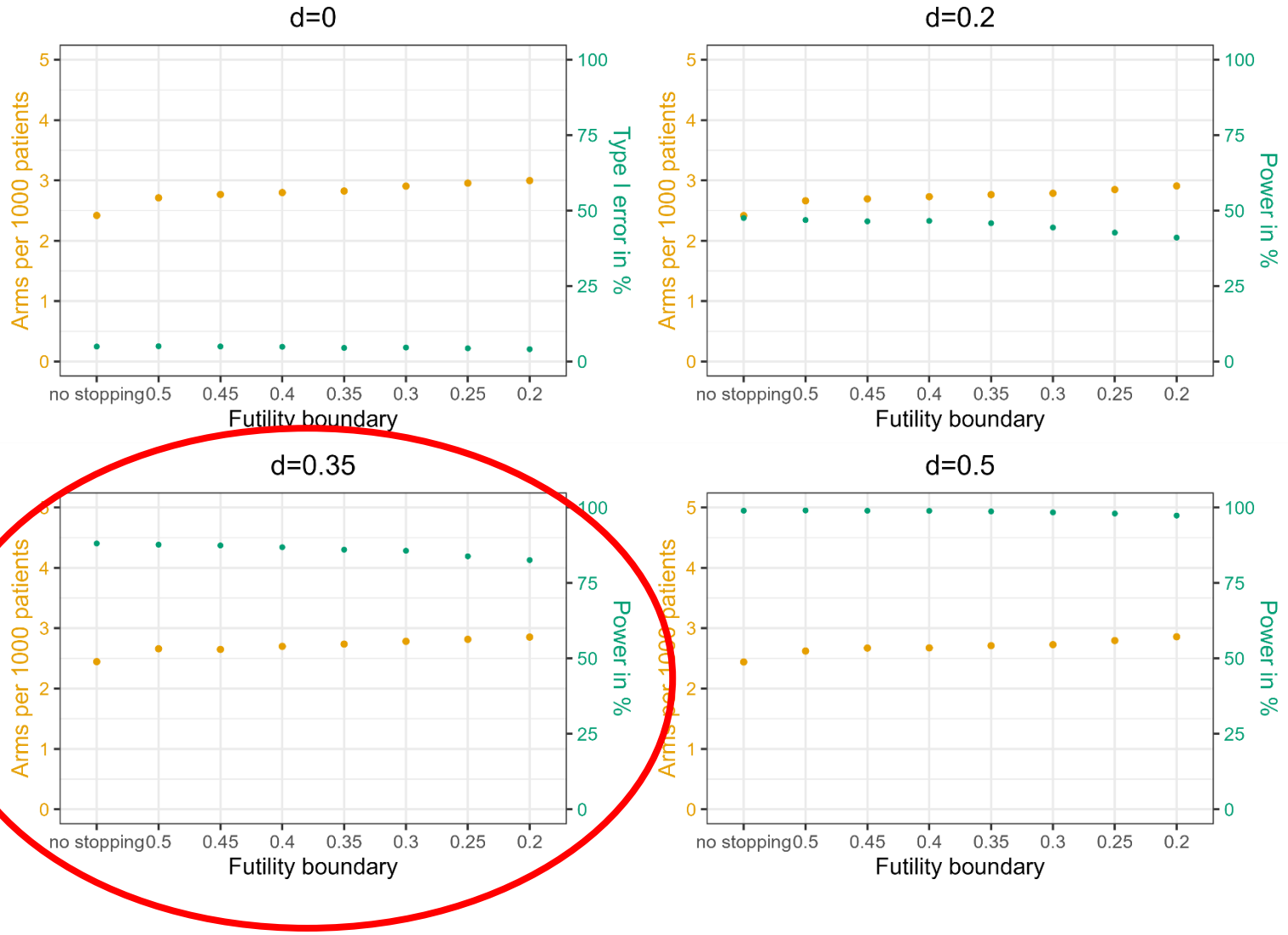
To stop or not to stop
-
Selecting a futility boundary

Selecting the Futility Boundary

More aggressive futility rules lead to:

- More arms tested
  (13 for no stopping, 14 for $\alpha_0 = 0.5$ and 15 for $\alpha_0 = 0.2$)
- Shorter duration of arms
- Smaller concurrent control arms

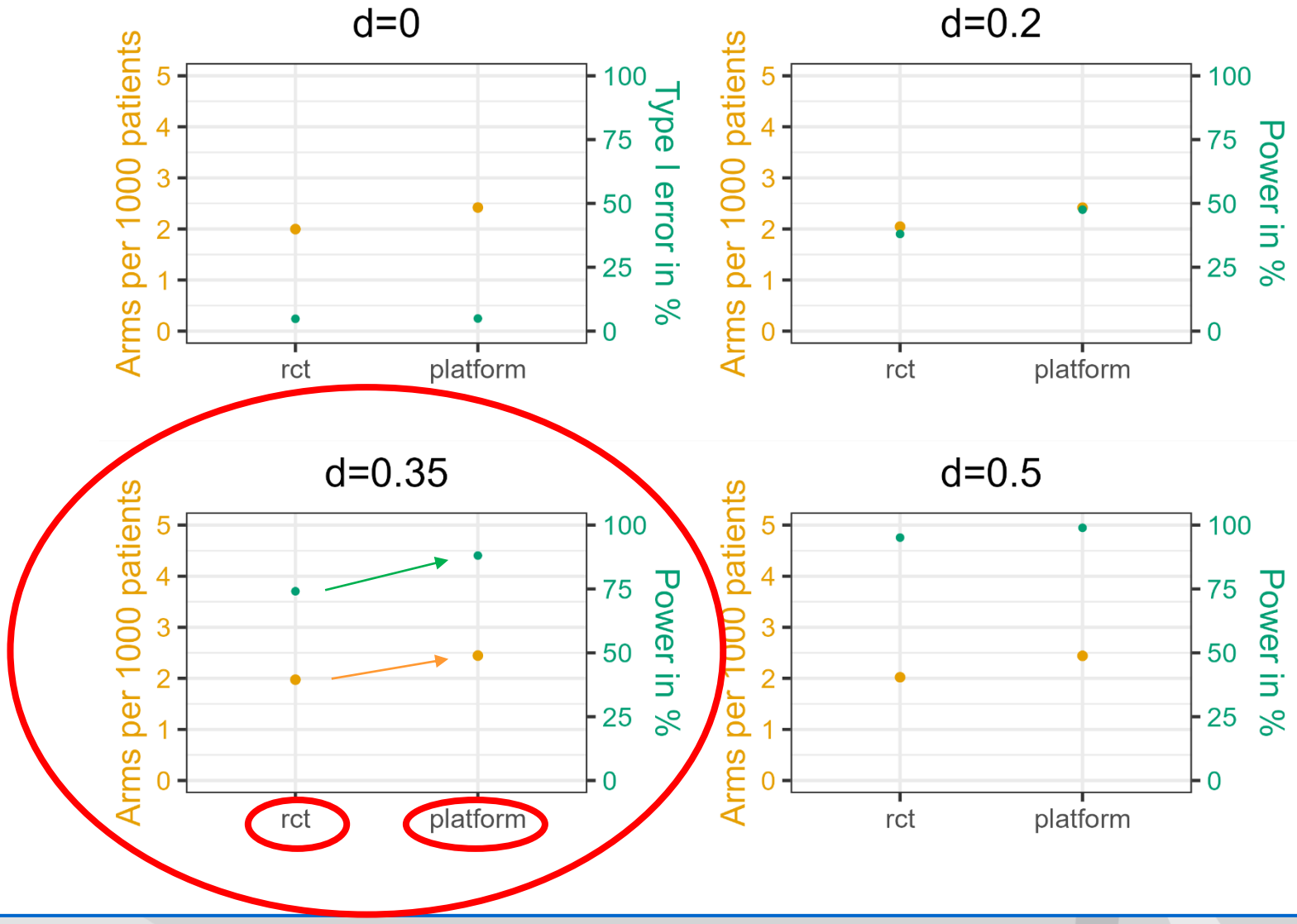
Futility: OCs for Success



Comparison to sequential RCTs with 1:1 allocation

Comparison to 1:1 RCT

For design without stopping for futility and minimal control cap of 0.35



Conclusion

- Increased statistical power
- More compounds tested
- Fewer participants on placebo
- Efficient use of infrastructure and resources
- “Customizable” to accommodate different preferences and risk tolerance

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Questions to you

- What would you regard as the biggest opportunities through platform trials?

- What would you regard as the biggest challenges in designing a platform trial?

Additional Slide: Selecting the Futility Boundary