Balancing events, not patients, maximizes power in randomized survival studies

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Pivotal survival trials

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Why?

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Schoenfeld's (1981) large sample approximation for the log-rank statistic:

$$Z \sim N(\theta\sqrt{p_0 p_1 d}, 1)$$

where

- θ: log hazard ratio (HR)
- p_j: proportion of patients randomized to arm j ($0 =$ control)
- d: number of events at final analysis

Why randomize patients 1:1?

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- ethics

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- statistical power
  - "1:1 maximizes power for continuous endpoints"
  - "1:1 maximizes power for survival endpoints" (Schoenfeld, 1981)

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  - HR > 0.4 (Barthel et al., 2006)
- "Reliable for typical hazard ratios under 1:1. Not so much under unequal randomization." (Yung et al.)

Alternative approximations for the log-rank statistic

	Randomization ratio that maximizes power (assuming fixed event size)
Schoenfeld (1981)	1:1
Freedman (1982)	$1/HR$
Rubinstein (1981)	that which results in balance of events (i.e., 1:1 event size ratio)

Research questions

I. What randomization ratio maximizes power?

II. When might unequal randomization be attractive, considering power, accrual duration, trial duration, and sample size?

I. What randomization ratio maximizes power?

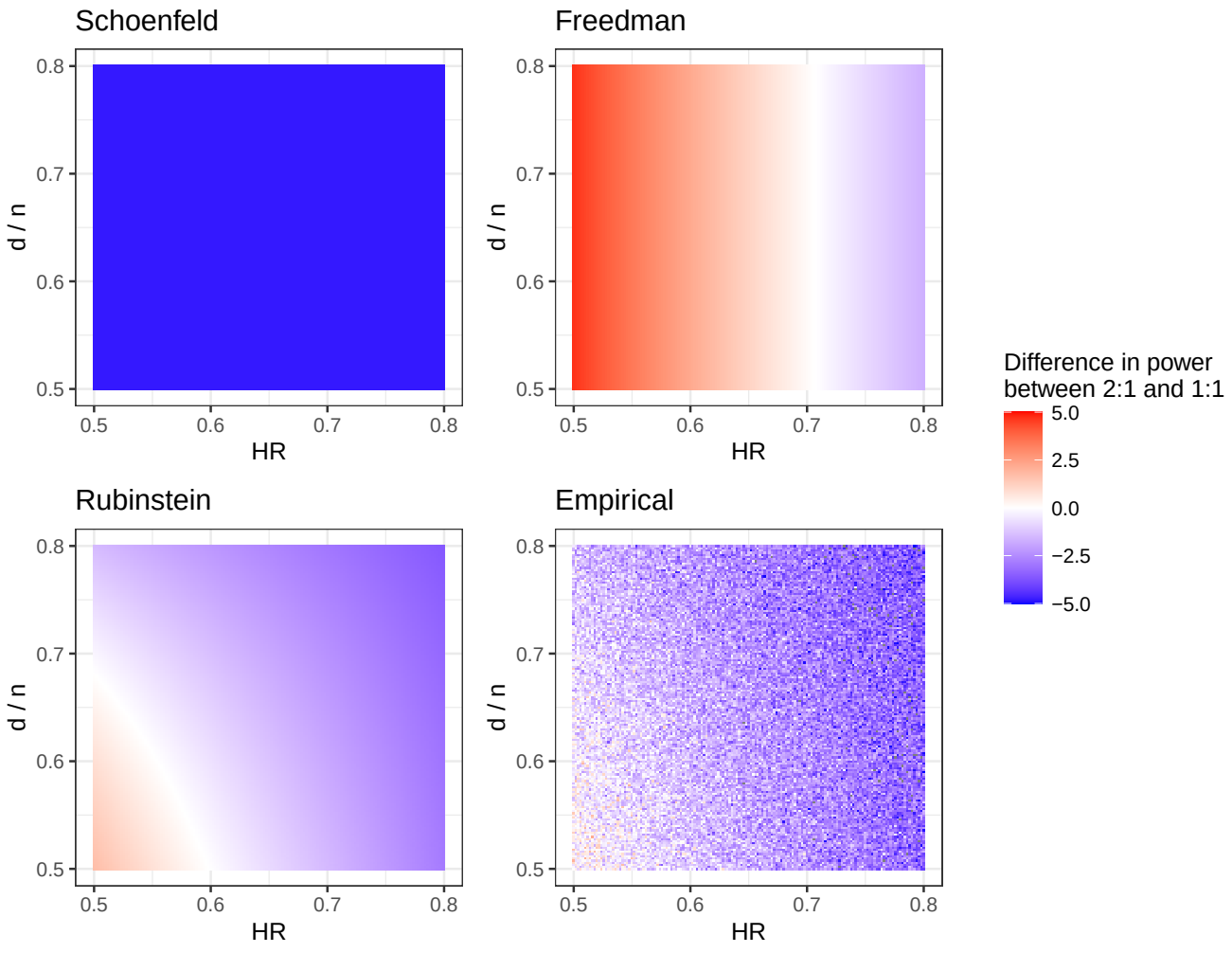
Given **hazard ratio** HR, **event-patient ratio** d/n, and **control median** CM=1y, we set ...

- **number of events** d based on Schoenfeld's equation with $p_0 = 0.5$, one-sided alpha 0.025, and 80% power
- **sample size** as $n = d * (d/n)^{-1}$
- **accrual rate** between 20-50 patients/month to ensure that trial duration is realistic

We then varied randomization ratio (**1:1, 3:2, 2:1**) and compared their power under various calculations (**Schoenfeld, Freedman, Rubinstein, empirical**).

Comparisons were made across the grid $(HR, d/n) \in [0.5, 0.8]^2$.

$$\text{Diff. in power} = \text{Power}(2{:}1, \text{Method}; \text{HR}, d/n) - \text{Power}(1{:}1, \text{Method}; \text{HR}, d/n)$$


Schoenfeld
Freedman
Rubinstein
Empirical
d / n
HR
0.5
0.6
0.7
0.8
Difference in power
between 2:1 and 1:1
5.0
2.5
0.0
−2.5
−5.0

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Protocol:

- 264 patients, randomized 1:1
- 189 OS events
- Median survival 11.4m vs. 7.0m (HR=0.61)
- two-sided $\alpha = 0.04$, 90% power
- 12m accrual duration, 24m trial duration

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Given 3:2 or 2:1 randomization, 6 alternatives total.

Design	RR, Description	d	n	Accrual Dur. (months)	Trial Dur. (months)
CM-017	1:1, Protocol	189	264	12.0	23.8
Alt 1	3:2, Prolonged study	190	(264)	(12.0)	24.9
Alt 2	3:2, Accelerated accrual	190	(264)	10.0	(23.8)
Alt 3	3:2, Increased enrollment	190	274	12.5	(23.7)
Alt 4	2:1, Prolonged study	198	(264)	(12.0)	27.6
Alt 5	2:1, Accelerated accrual	198	(264)	5.1	(23.8)
Alt 6	2:1, Increased enrollment	198	294	13.4	(23.8)

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Similar results were observed across a general set of scenarios:

- 3:2 minimal impact, easier to mitigate
- 2:1 greater impact, harder to mitigate

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- Fixing event size, power is maximized under 1:1 event size ratio (which depends on randomization, hazard, and event-patient ratio).
- 3:2 is a sensible option in most cases. Some additional patients can be randomized to the active arm with minimal impact on event size and trial duration.
- 2:1 may also be considered if event-patient ratio is small ($d/n \leq 0.5$). If event-patient ratio is large, then unequal randomization may be hard to justify given the increase in event size and trial duration.

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