THE OPTIMAL RANDOMIZATION RATIO IN TIME-TO-EVENT TRIALS IS NOT 1:1

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1. An unspoken but common misconception

- "Randomizing patients 1:1 optimizes statistical power."
- **TRUE** for continuous endpoint with equal variance.[1]
- **TRUE** for time-to-event endpoint under Schoenfeld's equation, a classical equation commonly used to calculate required event size in clinical trials.[2]
- **NOT TRUE** under alternative approximations for the large-sample distribution of the log-rank statistic!

2. Three approximations for the log-rank statistic

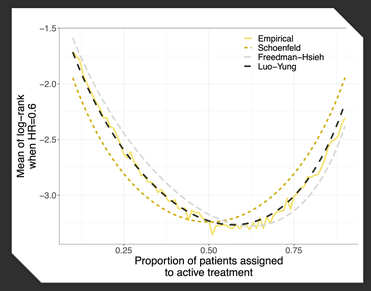
Assuming constant hazard ratio (HR), the recommended randomization ratio (RR) to optimize power differs depending on the approximation for the log-rank test.

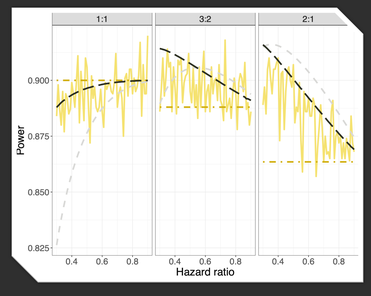
- **Schoenfeld** (1981) ⟹ RR=1
- Discussion on **Freedman** (1982) by Hsieh (1992) ⟹ RR=1/HR
- Discussion on **Luo et al.** (2018) by Yung and Liu (2019) ⟹ RR such that events are balanced across arms at the time of analysis

3. Comparing the three approximations: Mean and power

We consider a sequence of realistic, event-driven clinical trials with HRs between 0.3 to 0.9, T1E 0.05 two-sided, and 90% target power under 1:1. For each trial with unique HR, we vary the RR to explore its impact on power.

- Luo leads to the most accurate approximation in terms of both the sample mean and statistical power **(Fig 1-2)**.
- Schoenfeld's equation suggests that randomizing patients 3:2 and 2:1 decreases power by 1.2% and 3.7%.
- On the contrary, Luo's approximation indicates that **power can be maintained—perhaps even gained–when more patients are assigned to an active therapy (Fig 2).**





(Figures generated via R package **npsurvSS**.)

4. Recommended RR to maximize power given fixed sample and event size

- Luo's approximation is accurate and intuitive: **Balance the number of events, which is also the effective sample size in time-to-event setting**.
- See Table for rule of thumb to jumpstart considerations. Following this rule, unequal randomization will have similar power to 1:1.

Design HR	RR
0.7 to 1.0	1:1
0.5 to 0.7	3:2
Less than 0.5	2:1

5. Additional considerations

In practice, **many other factors should be taken into consideration when selecting a RR**. For example,

1. If the **risk-benefit ratio** is in favor of treatment, then patients stand to benefit from a higher chance of being assigned to treatment.
2. If unequal randomization is attractive to patients and leads to faster **accrual**, then overall timeline may be shortened. But if accrual is not accelerated, then overall timeline may be delayed.
3. Randomizing more patients to active treatment may accelerate time at which **"mature" data** is achieved.

References

1. Pocock, S. (1979) Allocation of Patients to Treatment in Clinical Trials. *Biometrics* 35:183-197.
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4. Hsieh, FY. (1992) "Comparing Sample Size Formulae for Trials with Unbalanced Allocating Using the Logrank Test." *Statistics in Medicine* 11:1091-1098.
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6. Yung, G and Liu, Y. (2019) "Sample Size and Power for the weighted Log-rank Test and Kaplan-Meier Based Tests with allowance for Nonproportional Hazards." *Biometrics.* doi:10.1111/biom.13196. (QR code available)