A Bayesian Perspective on the Two-Trials Rule

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$\rightarrow$ One-sided $p_1, p_2 \leq \alpha = 0.025$ in two independent trials.

$\rightarrow$ Overall T1E rate is $\alpha^2 = 0.025^2 = 0.000625$.

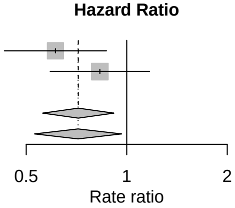
$\rightarrow$ Bound on partial T1E rate is $\alpha = 0.025$.

Example: The RESPIRE Trials

Chotirmall and Chalmers (2018)

- The RESPIRE 1 and 2 trials evaluated 32.5 mg ciprofloxacin dry powder inhalation (DPI) for the treatment of non-cystic fibrosis bronchiectasis.
  - RESPIRE 1 largely enrolled across Europe, North and South America, Australia and Japan
  - RESPIRE 2 focused on Asia and Eastern Europe
- Outcome: Frequency of exacerbations within 14-days
- Result: $p_1 = 0.003$, $p_2 = 0.14$

Study	logHR	SE(logHR)	HR	95%−CI	Weight (common)	Weight (random)
1	−0.4916	0.1798	0.61	[0.43; 0.87]	48.6%	49.0%
2	−0.1853	0.1747	0.83	[0.59; 1.17]	51.4%	51.0%
Common effect model			**0.72**	**[0.56; 0.92]**	**100.0%**	**--**
Random effects model			**0.71**	**[0.53; 0.97]**	**--**	**100.0%**



Heterogeneity: $I^2 = 33\%$, $\tau^2 = 0.0155$, $p = 0.22$

Null Hypotheses and Type-I Error Rates

Study-specific null hypotheses $H_0^1\colon \theta_1 = 0$ and $H_0^2\colon \theta_2 = 0$

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is a point null hypothesis.

$\rightarrow$ Overall T1E rate

2. The no-replicability or union null hypothesis

$$H_0^1 \cup H_0^2$$

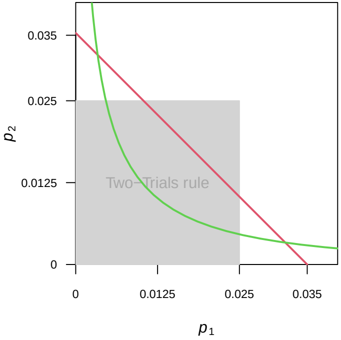
is a composite null hypothesis.

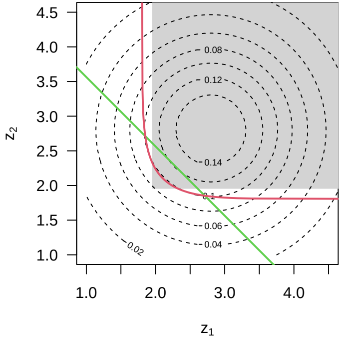
$\rightarrow$ Partial T1E rate

Beyond the Two-Trials Rule

Two alternatives with same overall T1E rate

1. Edgington's method: $p_1 + p_2 \leq \sqrt{2}\,\alpha \approx 0.035$ (Edgington, 1972)
2. Pooled-trials rule: $z_1 + z_2 \geq \sqrt{2}\,z_{1-\alpha^2} \approx 4.56$ (Senn, 2021)

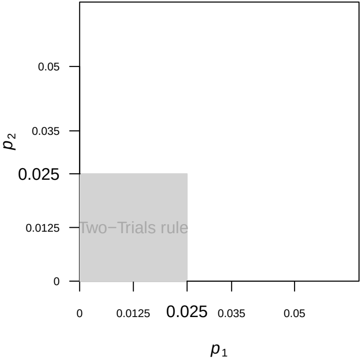




Contour lines represent the distribution of Z_1 and Z_2 under H_1 for 80% power.

Bounds on Partial T1E Rate

Overall T1E control at level 0.025^2



Method	Bound on partial T1E rate
Two-trials rule	0.025

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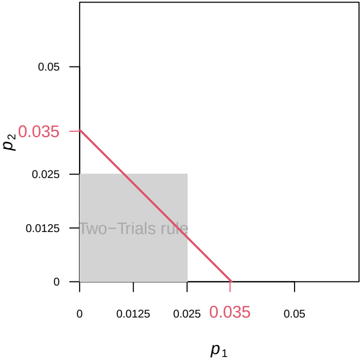

Method	Bound on partial T1E rate
Two-trials rule	0.025
Edgington	0.035

Beyond the Two-Trials Rule

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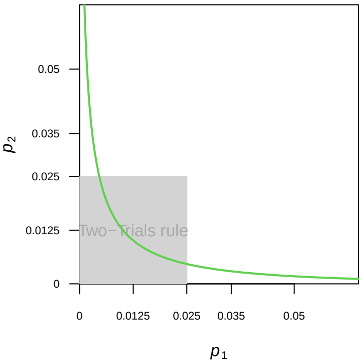

Method	Bound on partial T1E rate
Two-trials rule	0.025
Edgington	0.035
Pooled	1.00

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Project Power

Assume both trials are powered to detect common true effect:

Method	Trial power (%) 80	90
Two-trials rule	64	81

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Method	80	90
Two-trials rule	64	81
Edgington	68	84
Pooled	77	91

A Bayesian Perspective

- Frequentist focus on error rates
- A Bayesian quantifies the evidence in terms of the Bayes factor BF:
  1. Alternative against intersection null
  2. Alternative against union null
- We compare the three methods based on the smallest Bayes factor that can lead to success: $\min_{\text{success}} \text{BF}$
- $\min_{\text{success}} \text{BF}$ should be large to ensure sufficient evidence under success.

Bayes Factors
Intersection null

- Idea: Use Bayes factors based on test statistics Z_1, Z_2
- Assume: Same design for both trials $\rightarrow$ same power, same sample size

$\rightarrow$ Sufficient statistic $\bar{Z} = (Z_1 + Z_2)/2$ with

$$\begin{aligned} \bar{Z} \mid H_0 &\sim \text{N}(0, 1/2) \text{ under intersection null} \\ \bar{Z} \mid H_1 &\sim \text{N}(\mu, 1/2 + \tau^2) \text{ under } H_1 \\ \text{BF} &= f(\bar{Z} \mid H_1)/f(\bar{Z} \mid H_0) \end{aligned}$$

$\mu = \Phi^{-1}(1 - \alpha) + \Phi^{-1}(1 - \beta)$ is a function of the individual trial power $1 - \beta$.

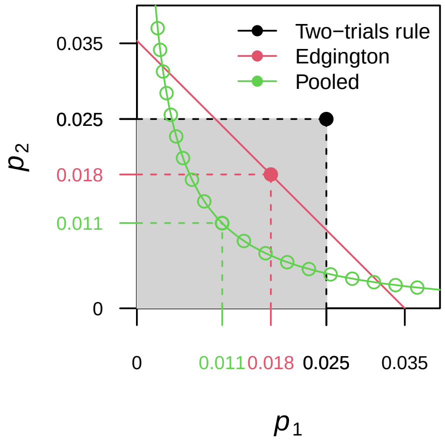
- Implicit normal prior with variance τ^2 on μ
- RESPIRE with 90% power:

BF	Prior
6.0	point prior ($\tau^2 = 0$)
11.0	normal prior ($\tau/\mu = 0.25$)

Smallest Bayes Factor That Can Lead to Success

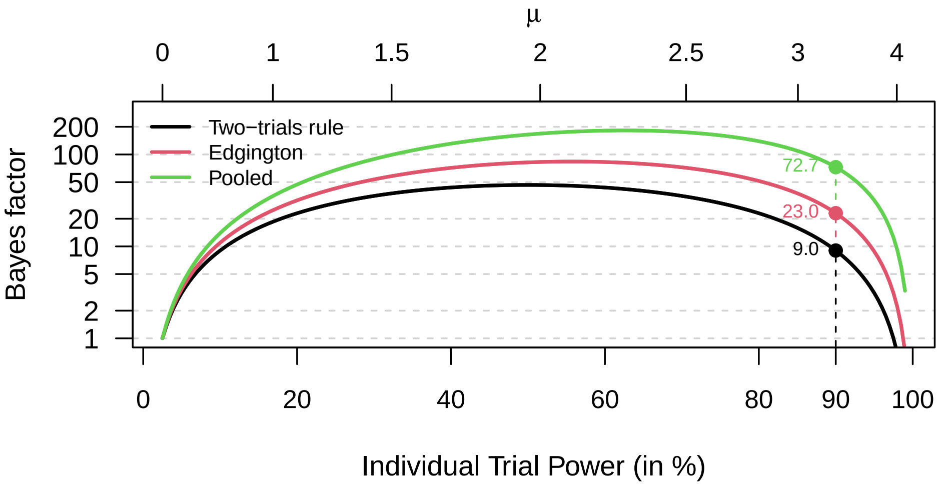
Intersection null

Where is the smallest Bayes factor that can lead to success?



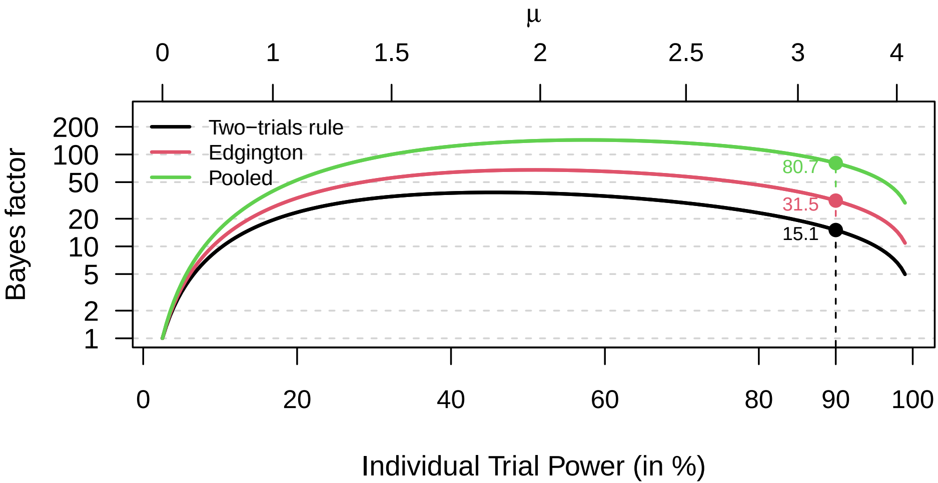
Smallest Bayes Factor That Can Lead to Success

Intersection null Bayes factors with point prior



Smallest Bayes Factor That Can Lead to Success

Intersection null Bayes factors with normal prior



Bayes Factors
Union null

- Prior-predictive distribution under union null:

$$
\begin{aligned}
Z_1, Z_2 &\sim \text{N}(0, 1) \text{ with probability } 1/3 \\
Z_1 &\sim \text{N}(\mu, 1 + \tau^2) \text{ and } Z_2 \sim \text{N}(0, 1) \text{ with probability } 1/3 \\
Z_1 &\sim \text{N}(0, 1) \text{ and } Z_2 \sim \text{N}(\mu, 1 + \tau^2) \text{ with probability } 1/3
\end{aligned}
$$

- RESPIRE with 90% power:

BF	Prior
3.4	point prior
7.5	normal prior

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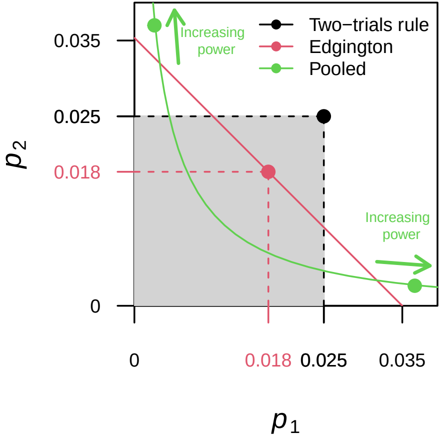
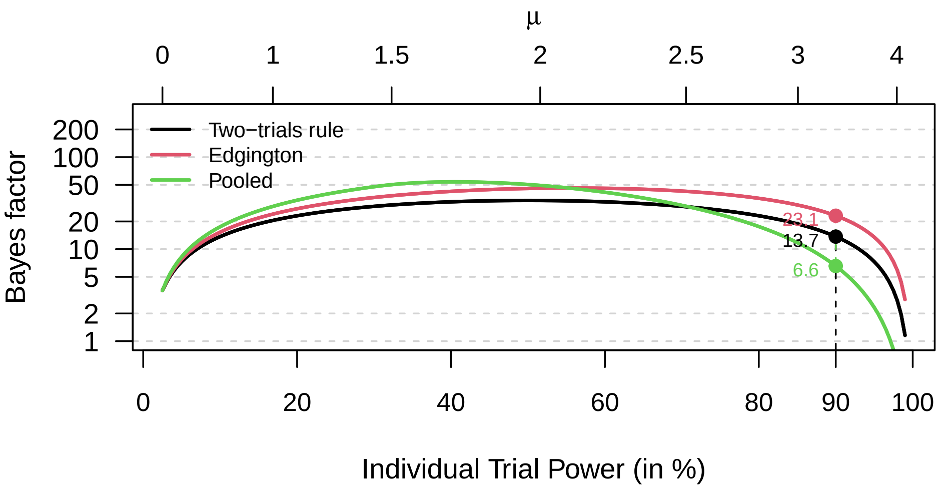


Smallest Bayes Factor That Can Lead to Success

Union null Bayes factors with point prior



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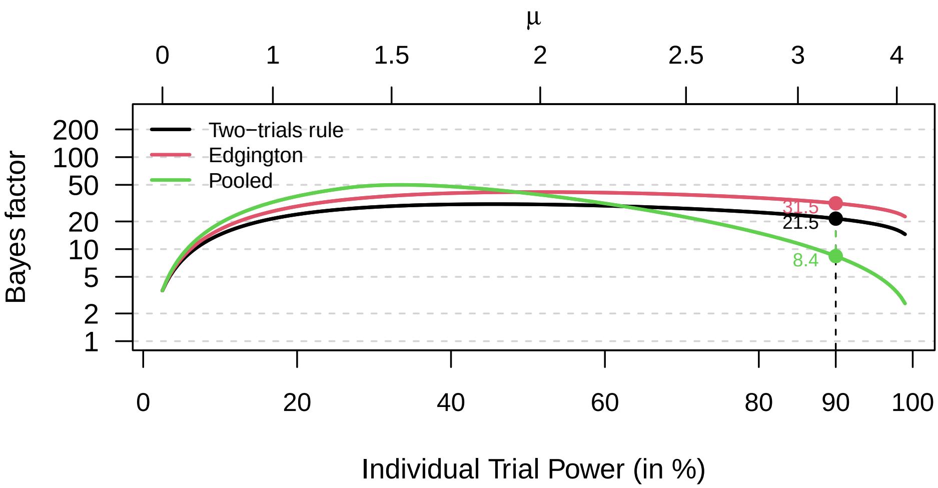

Summary

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Idea: Compare $\min_{\text{success}}$ BF to ensure sufficient evidence under success

1. Edgington always better than two-trials rule
2. Pooled-trials-rule best for intersection null, but not for union null
3. Edgington best under union null for reasonably powered alternatives

References

Chotirmall, S. H. and Chalmers, J. D. (2018). RESPIRE: breathing new life into bronchiectasis. European Respiratory Journal, 51(1):1702444.

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