Adaptive Monitoring: Optimal wait-time to control false discoveries

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Overview

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AM SGPV Adaptive monitoring on Second Generation p-Value (Chipman 2019)

Burn-in To ensure $\alpha < 0.05$ with unlimited sample size

Prematurely Ending Clinical Trial(s)

Towards a Revolution in COPD Health (TORCH) (Calverley 2007)

Primary Aim: Establish whether beta-agonist (salmeterol plus fluticasone propionate) has survival benefit in participants with chronic obstructive pulmonary disease

2007 6112 participants

- HR 0.825 (95% CI: 0.681-1.002, p-adjusted=0.052)
- Awkward Conclusion: primary outcome did not reach statistical significance, yet 'significant benefits in all other outcomes.'

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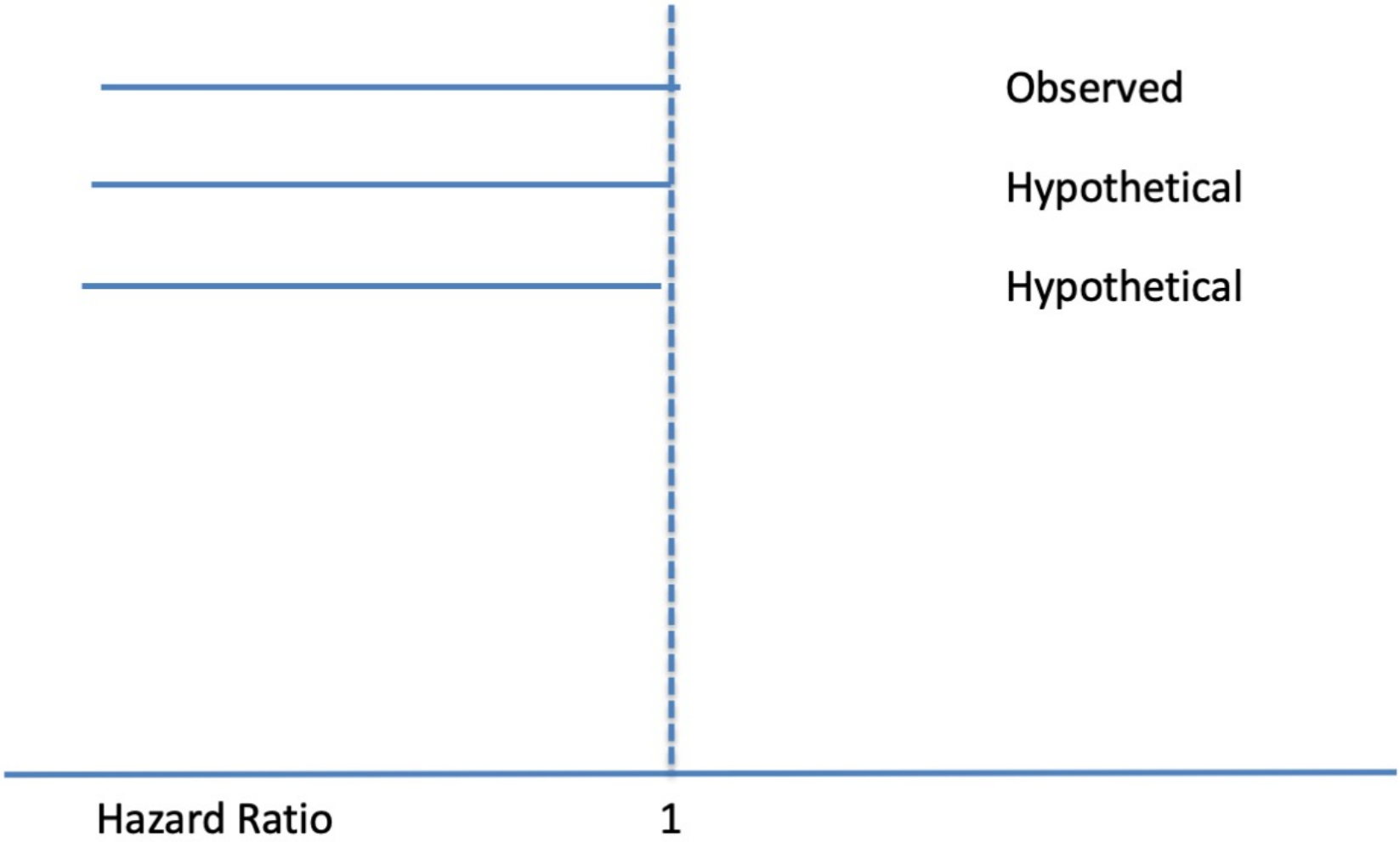
- Awkward Conclusion: primary outcome did not reach statistical significance, yet 'significant benefits in all other outcomes.'

Envisioning treatment effects



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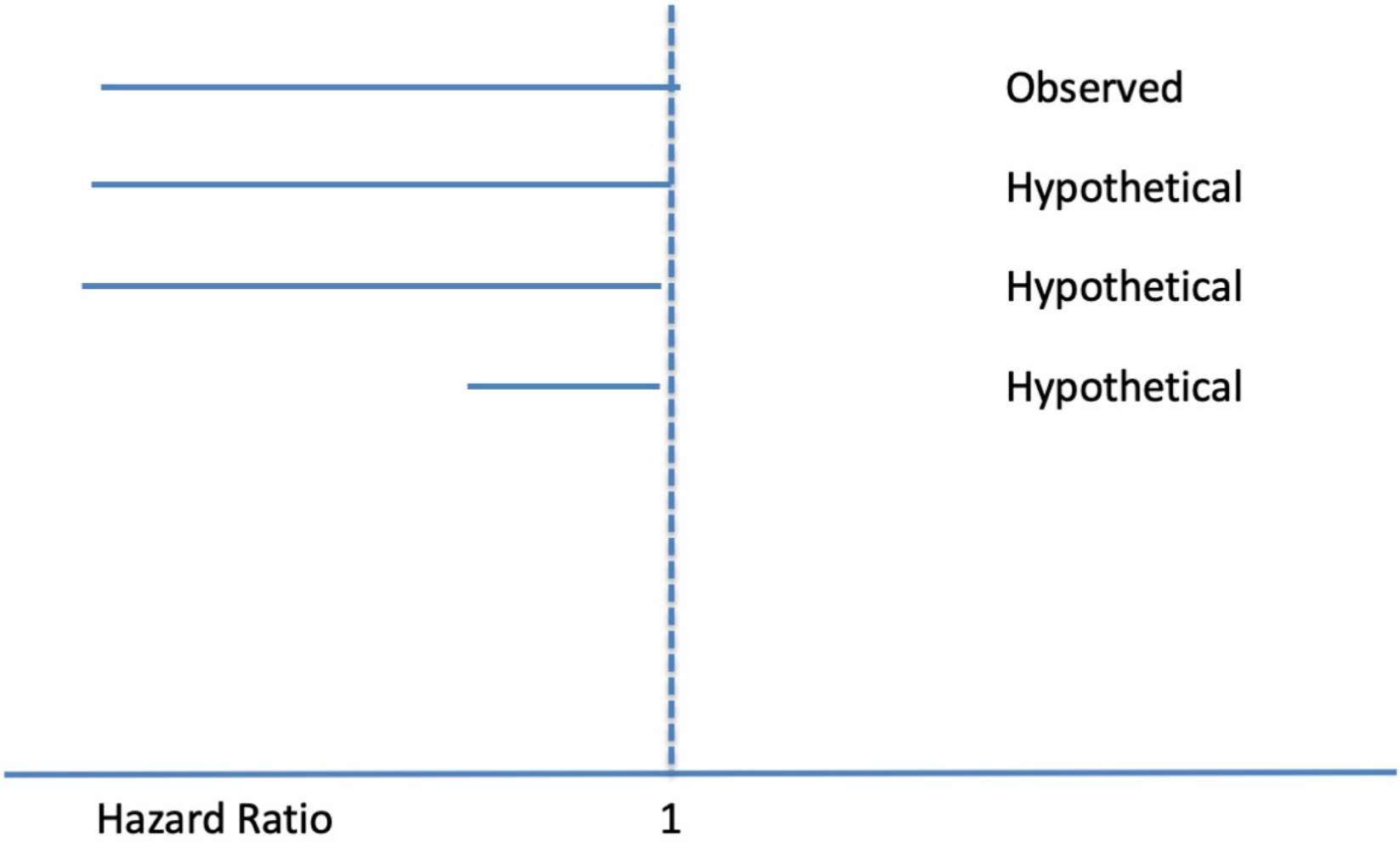
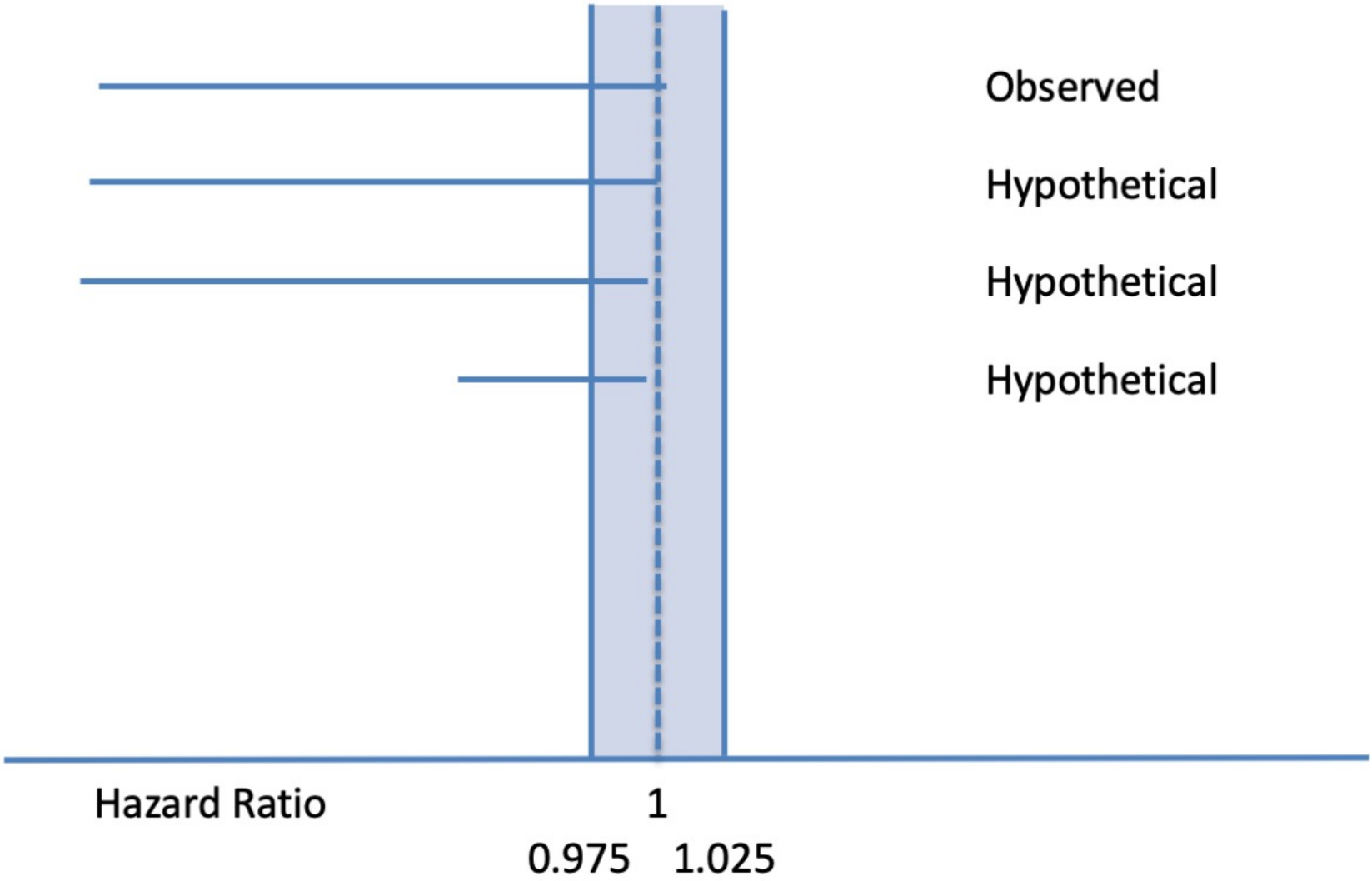


Region of Practically Equivalent Effects (ROPE) (Kruschke 2011)



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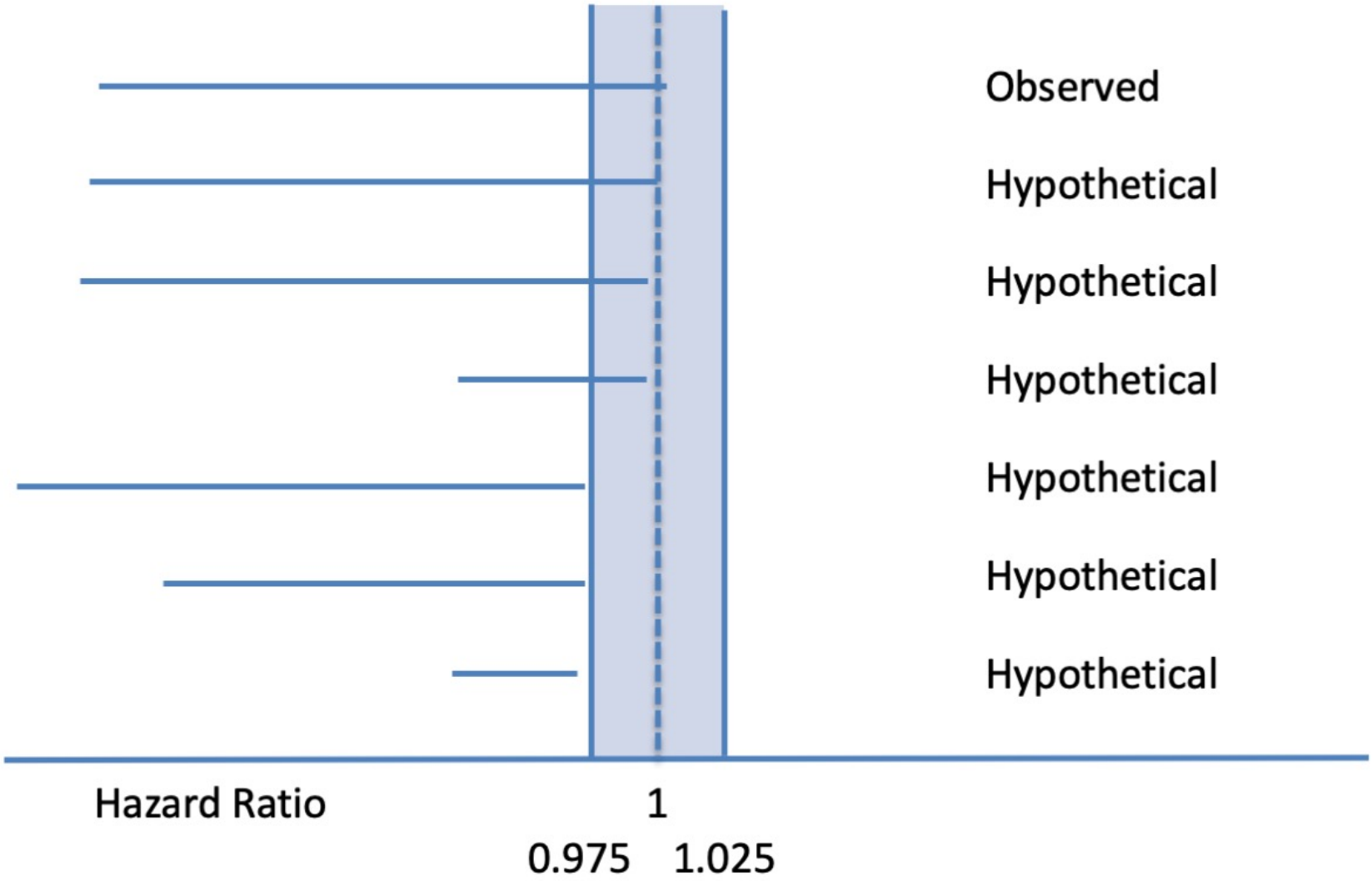
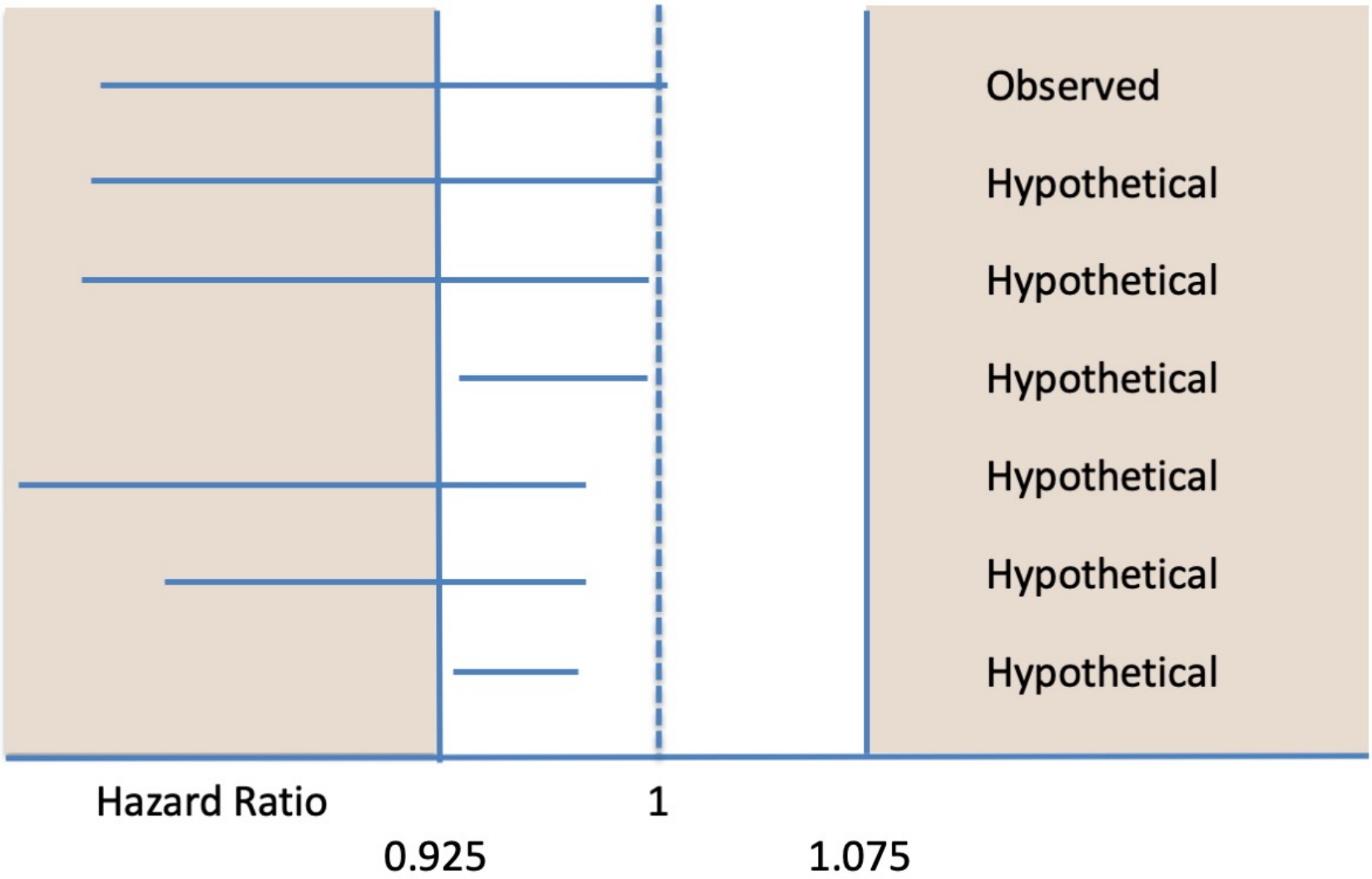
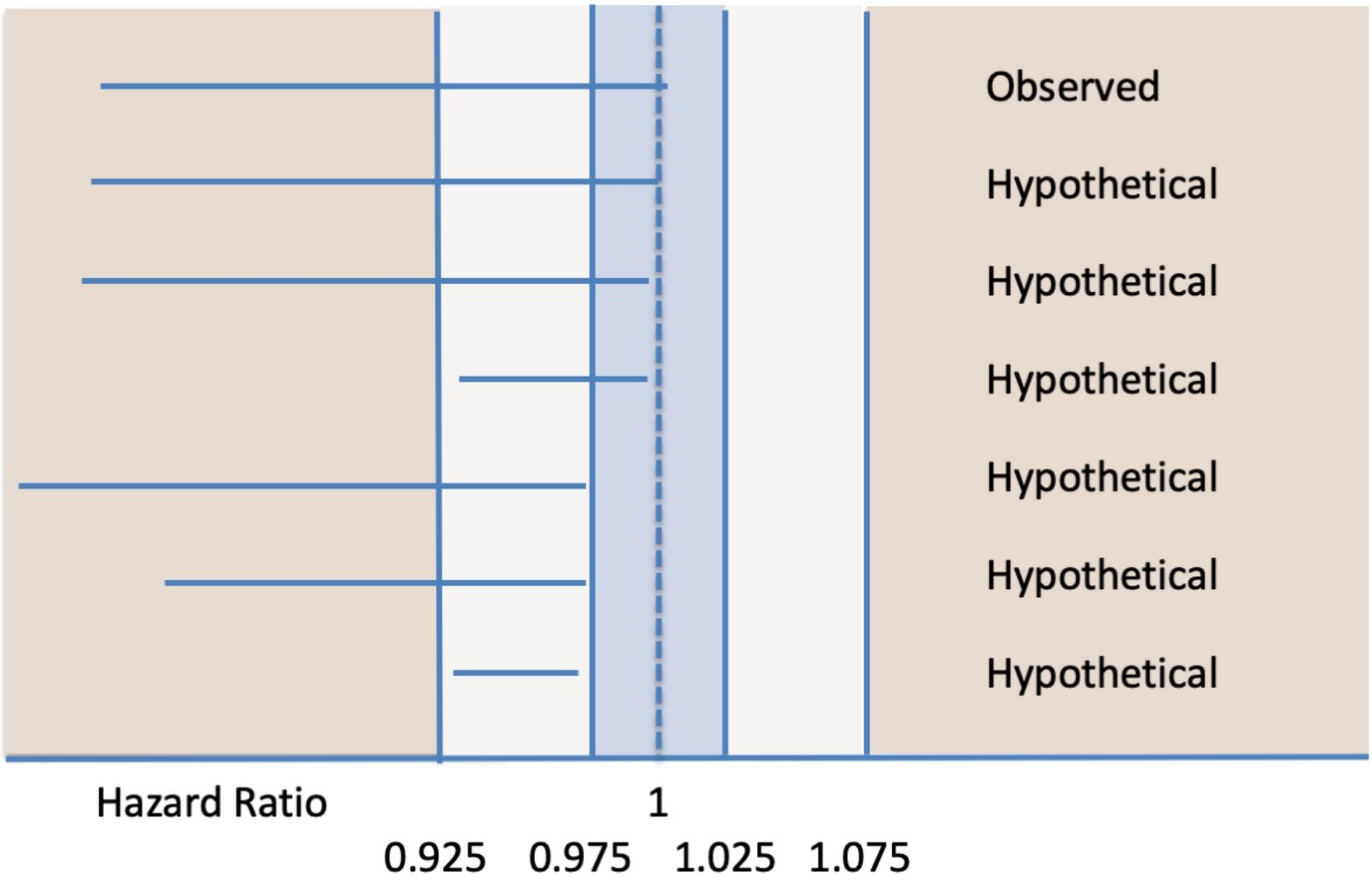


Region of Meaningful Effects (ROME)

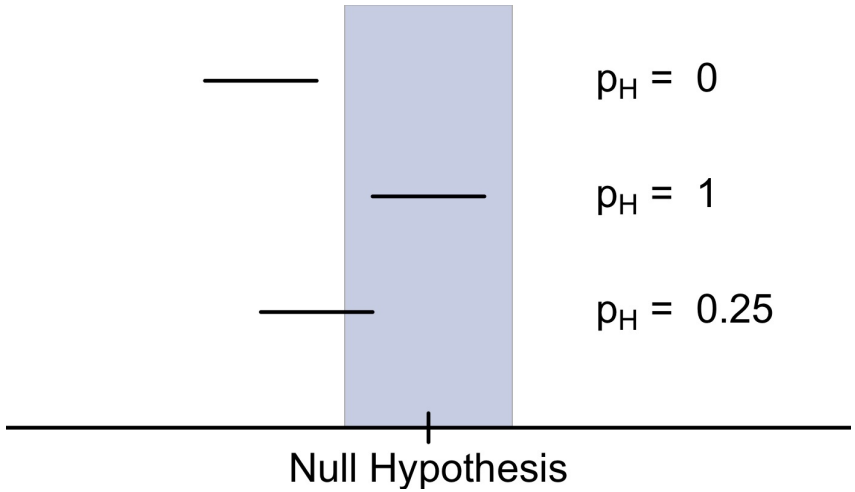


ROPE and ROME



Second Generation p-value (SGPV; Blume et al. 2018, 2019)

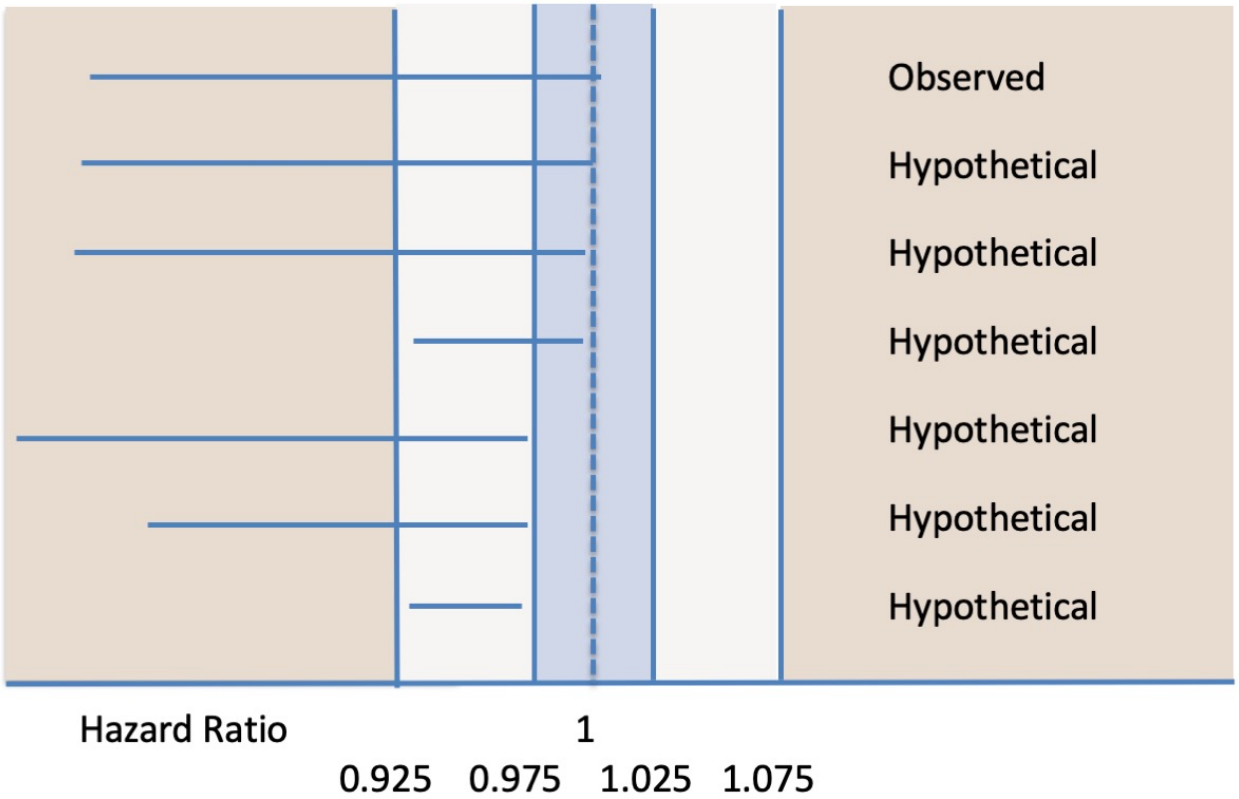
What proportion of interval overlaps with Δ_H?



Interpretation of p_H

- $p_H = 0$: Evidence to rule out hypothesis effects
- $p_H = 1$: Evidence supporing hypothesis effects
- $0 < p_H < 1$: Inconclusive, need more data

TORCH with ROPE and ROME



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Adaptive Monitoring with SGPV

Wait	Interval width stabilizes
Monitor	Interval and SGPV at desired looks
Alert	$p_{ROPE} = 0.0$: Ruled out ROPE effects
	$p_{ROME} = 0.0$: Ruled out ROME effects
Affirm	Stop if same conclusion k participants later
	End of resources
Report	Only the final interval when stopping

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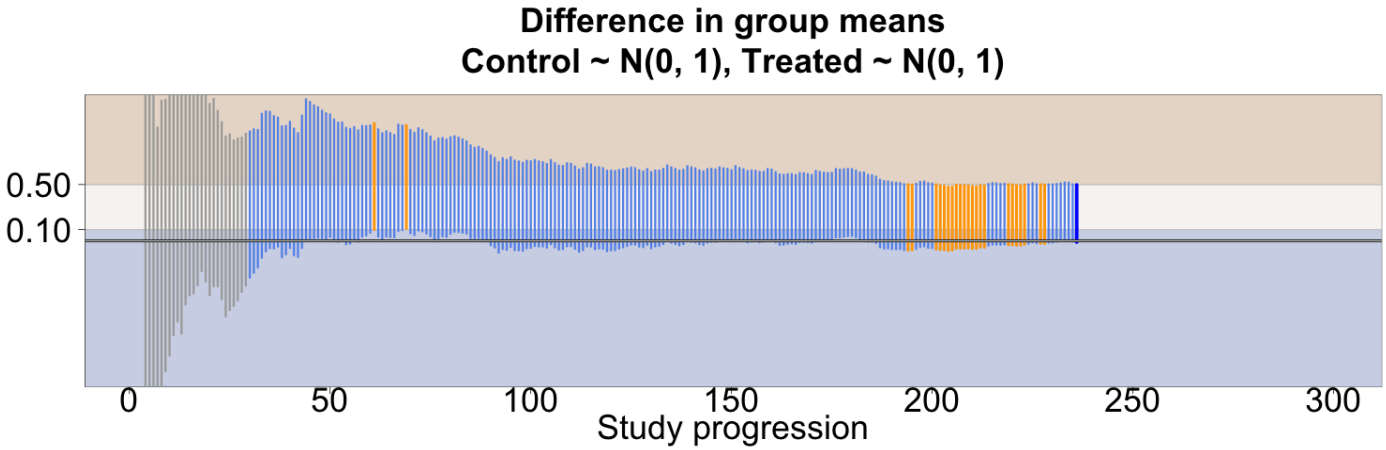

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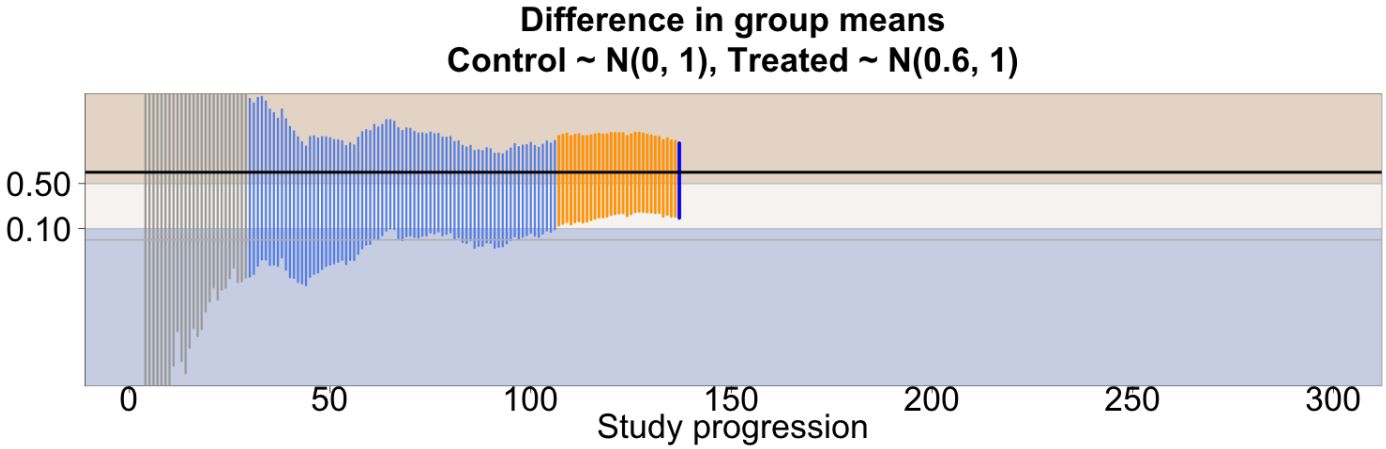

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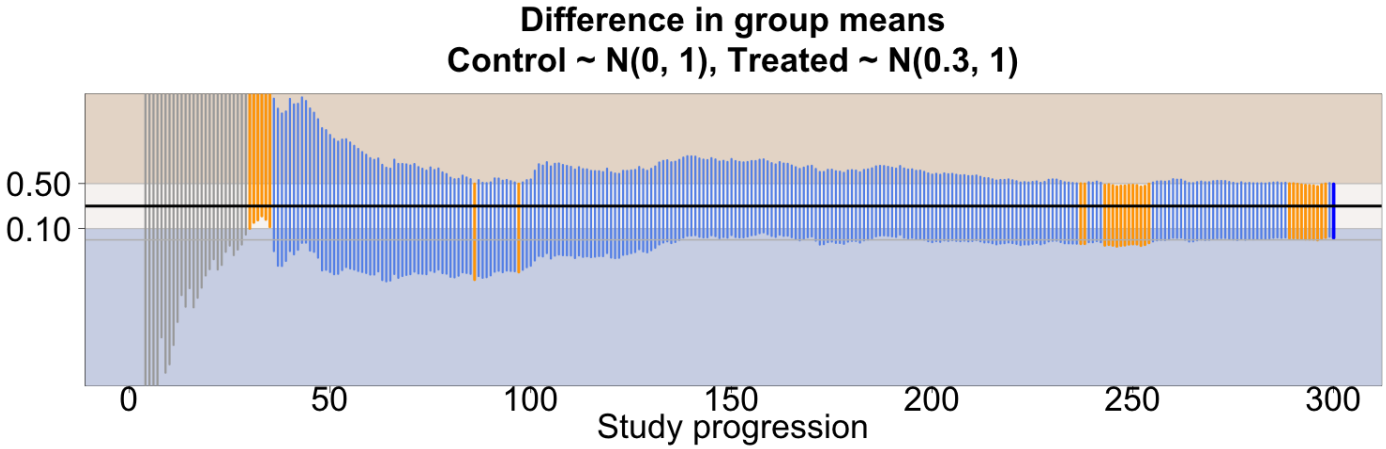

Error probabilities

Error probabilities (such as Type I Error) depend on

- ROPE and ROME
- Wait time
- Affirmation steps (k)

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- ROPE and ROME (set by science)
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Wait time with unlimited sample size

- Measured by inferential width

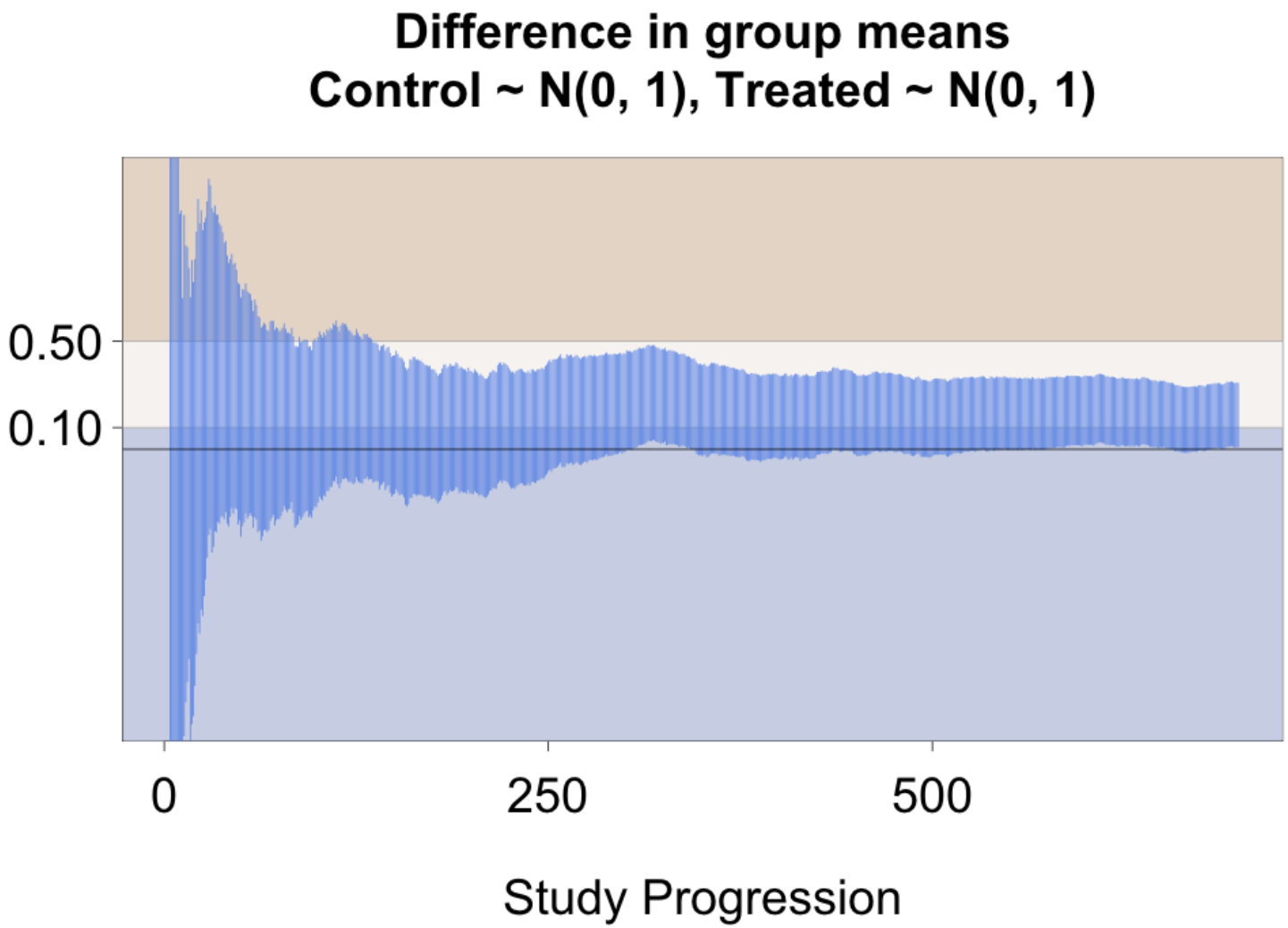
Controlling errors

Simulations with 40K replicates with varying wait times

Holding constant:

- Control~N(0,1), Treated~N(0,1)
- ROME and ROPE regions (10 settings)
- $k = 0$

How long to wait before applying monitoring rules: A one-sided example



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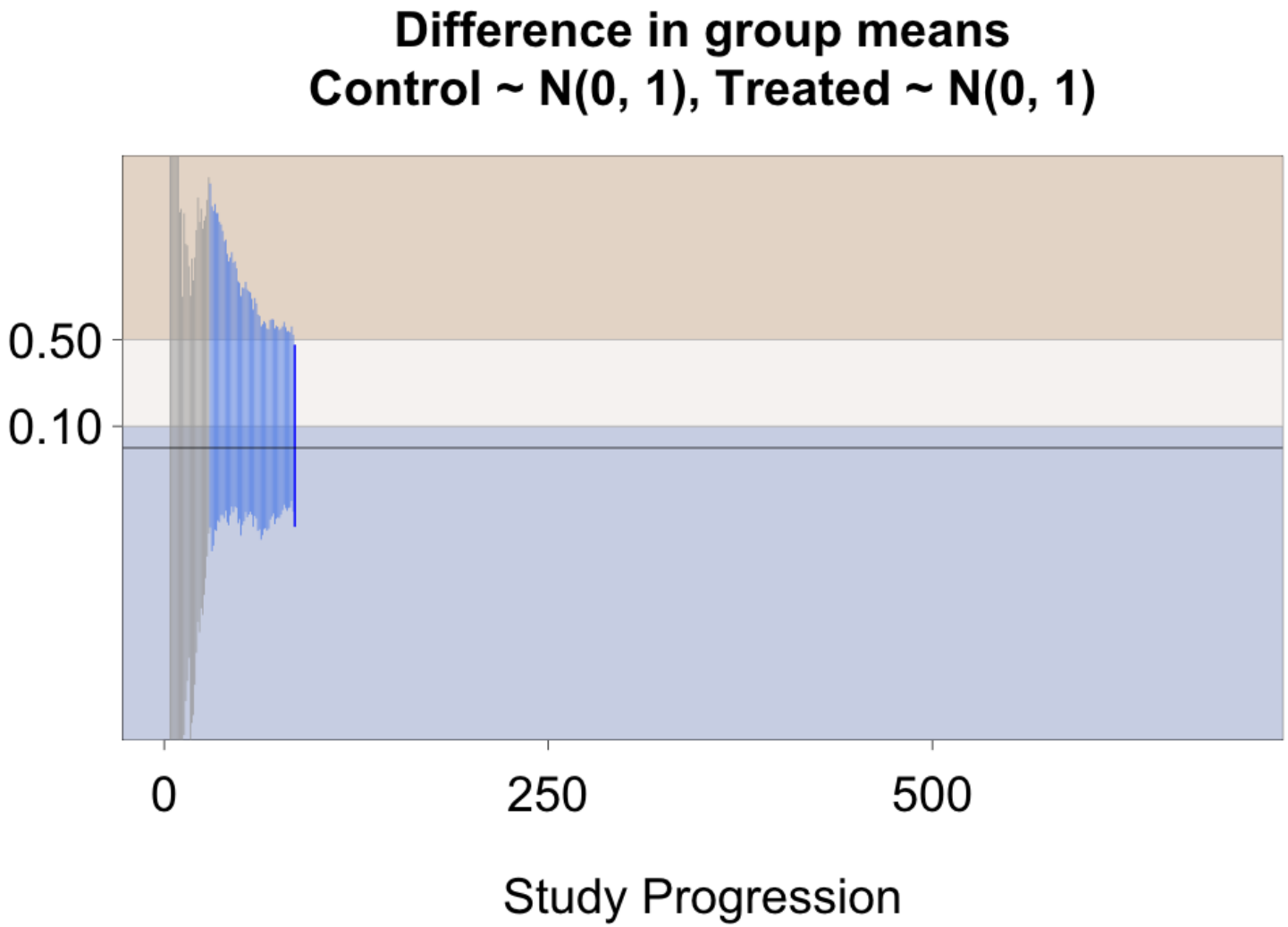

Wait until expected margin if error (1/2 width of CI) is 0.5

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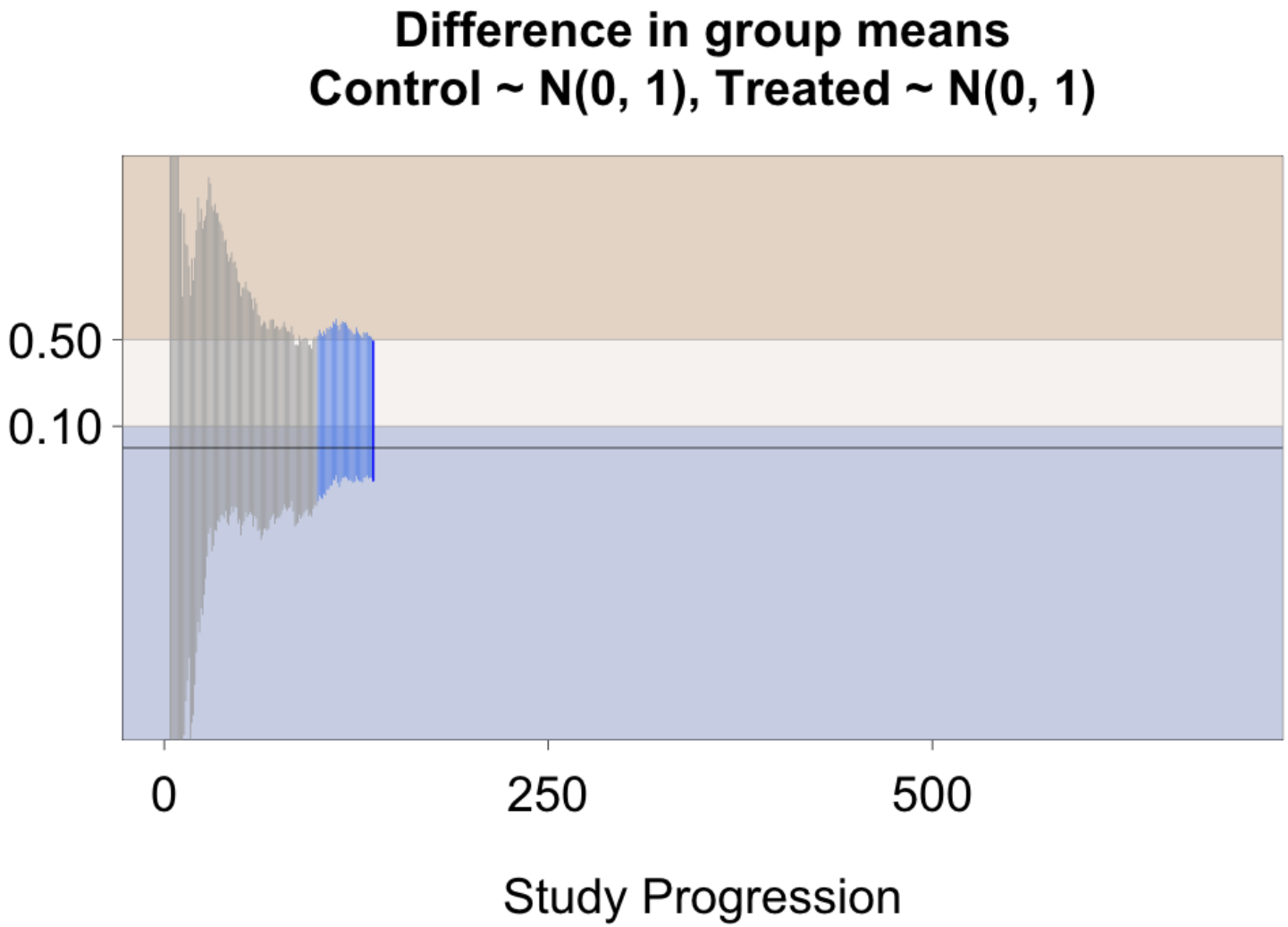

Wait until expected margin if error (1/2 width of CI) is 0.25

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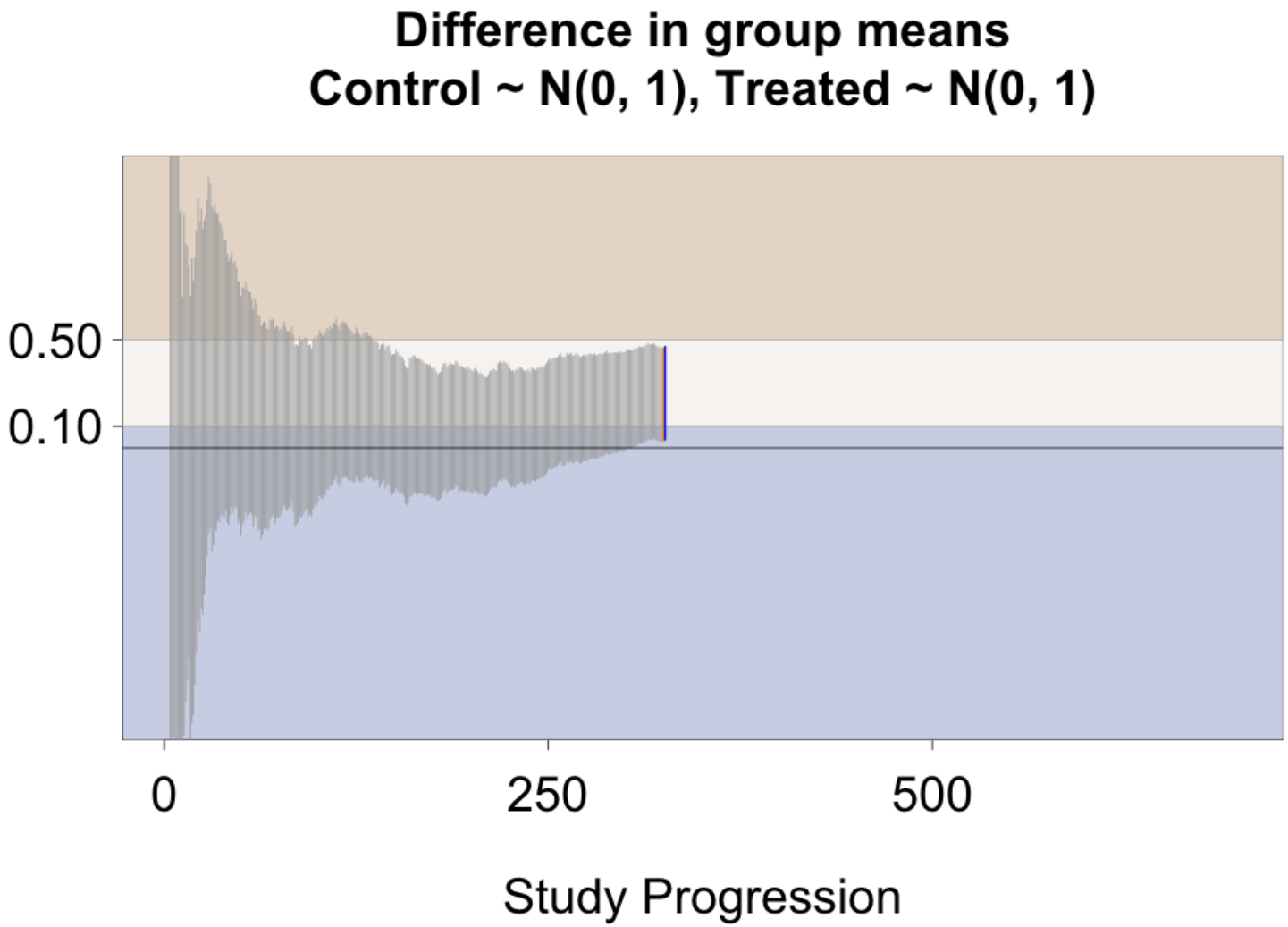
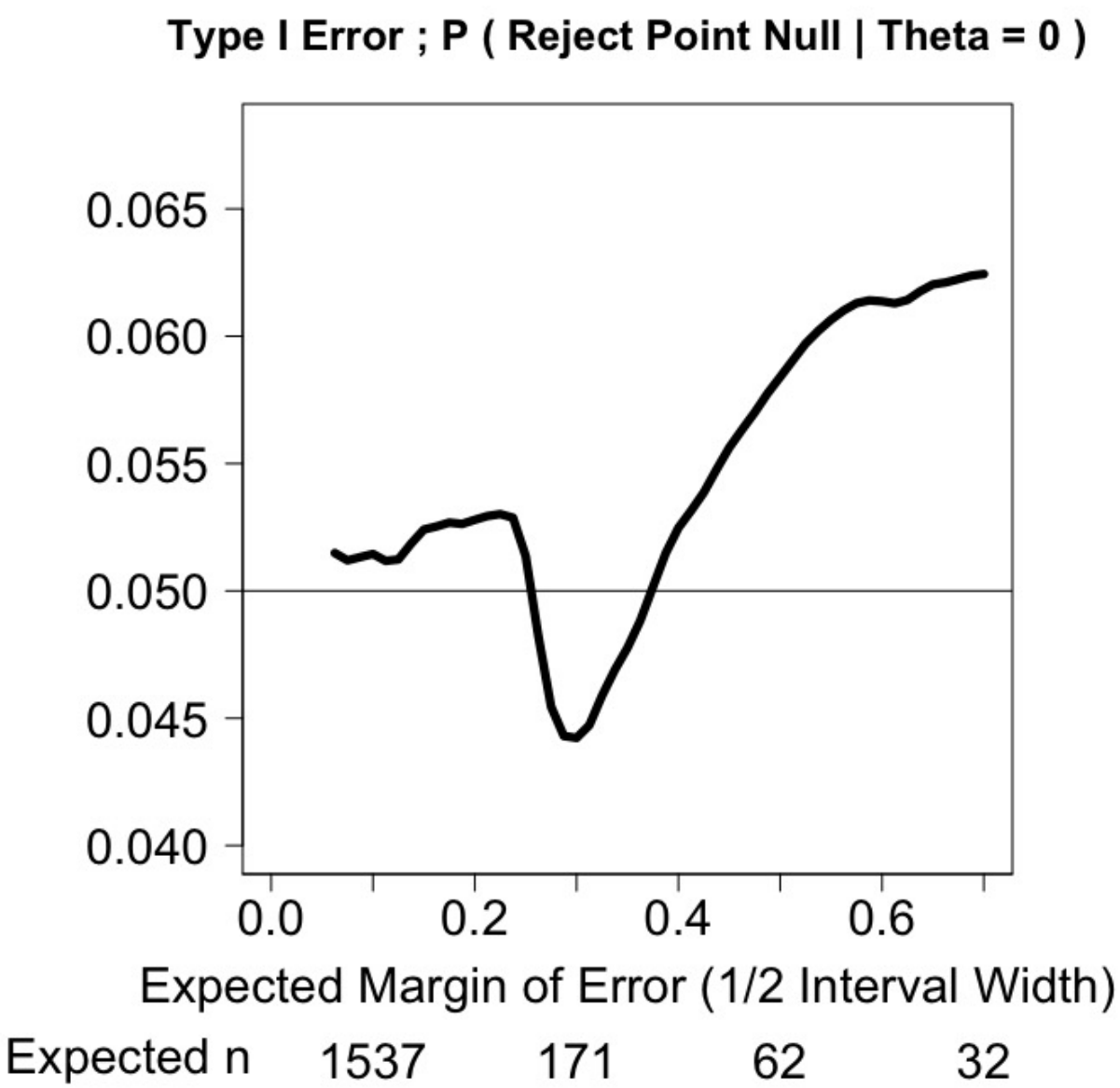
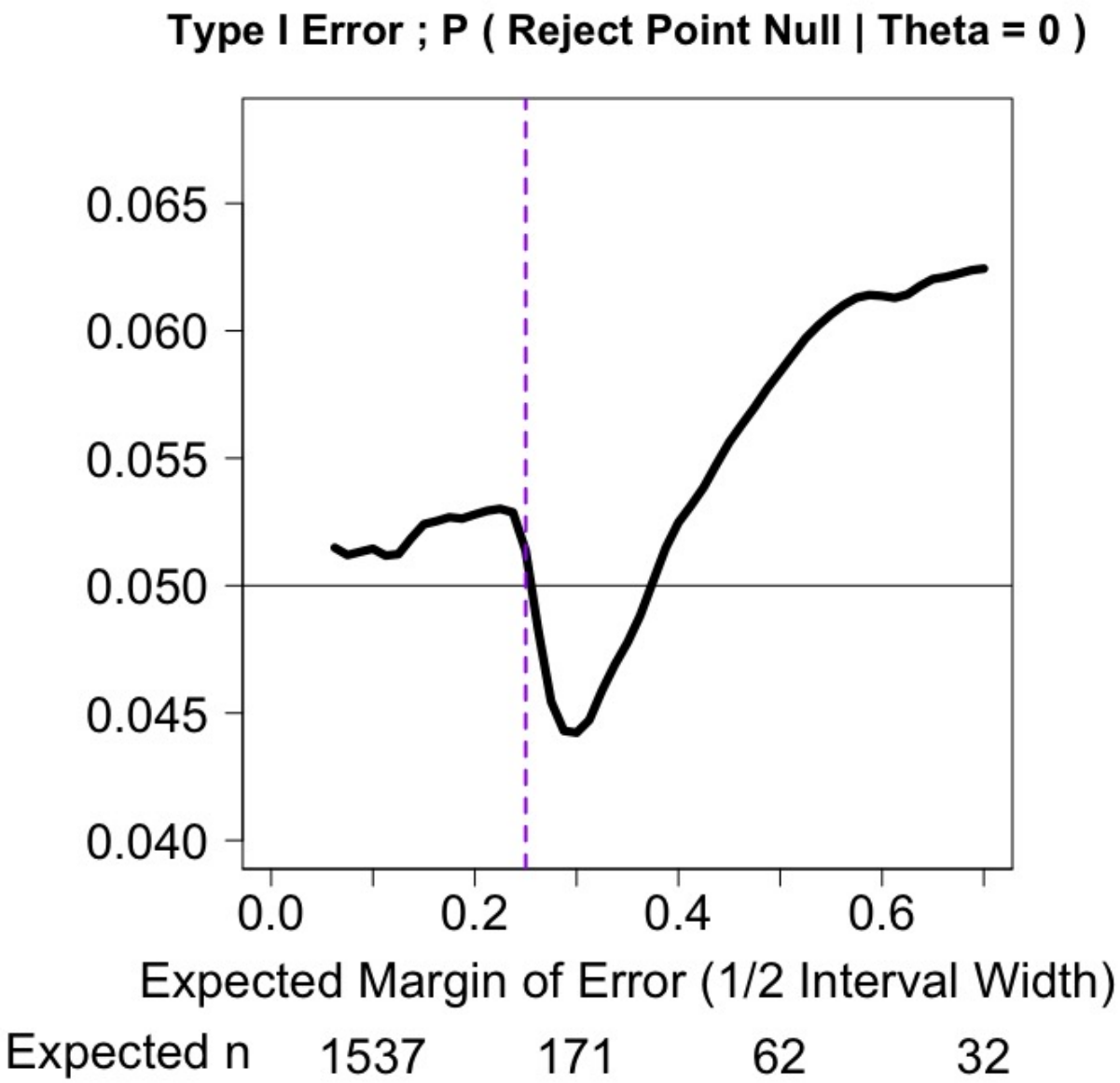


Wait until expected margin if error (1/2 width of CI) is 0.15

Type I Error


Type I Error ; P (Reject Point Null | Theta = 0)
0.065
0.060
0.055
0.050
0.045
0.040
0.0
0.2
0.4
0.6
Expected Margin of Error (1/2 Interval Width)
Expected n
1537
171
62
32

Type I Error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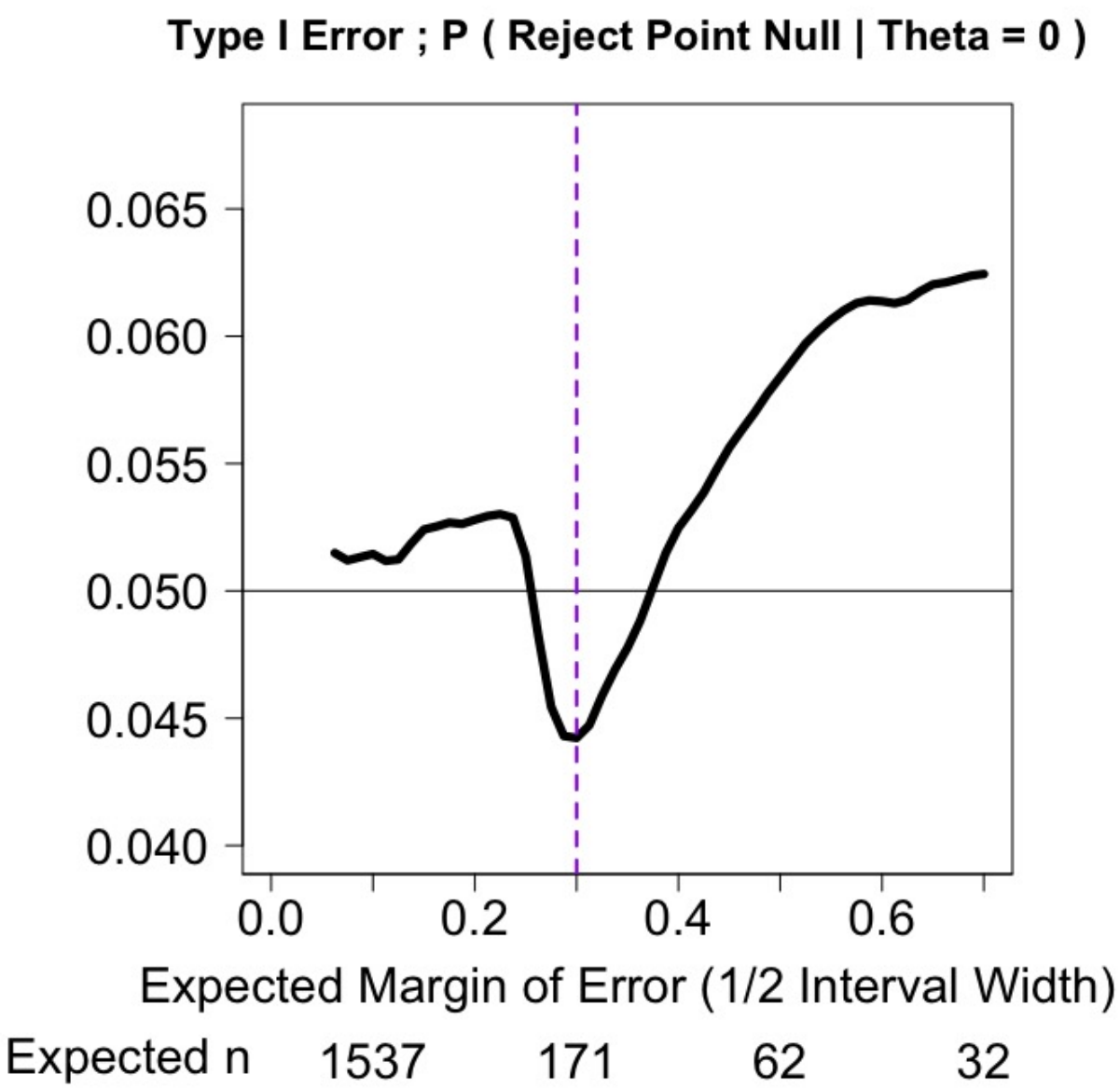
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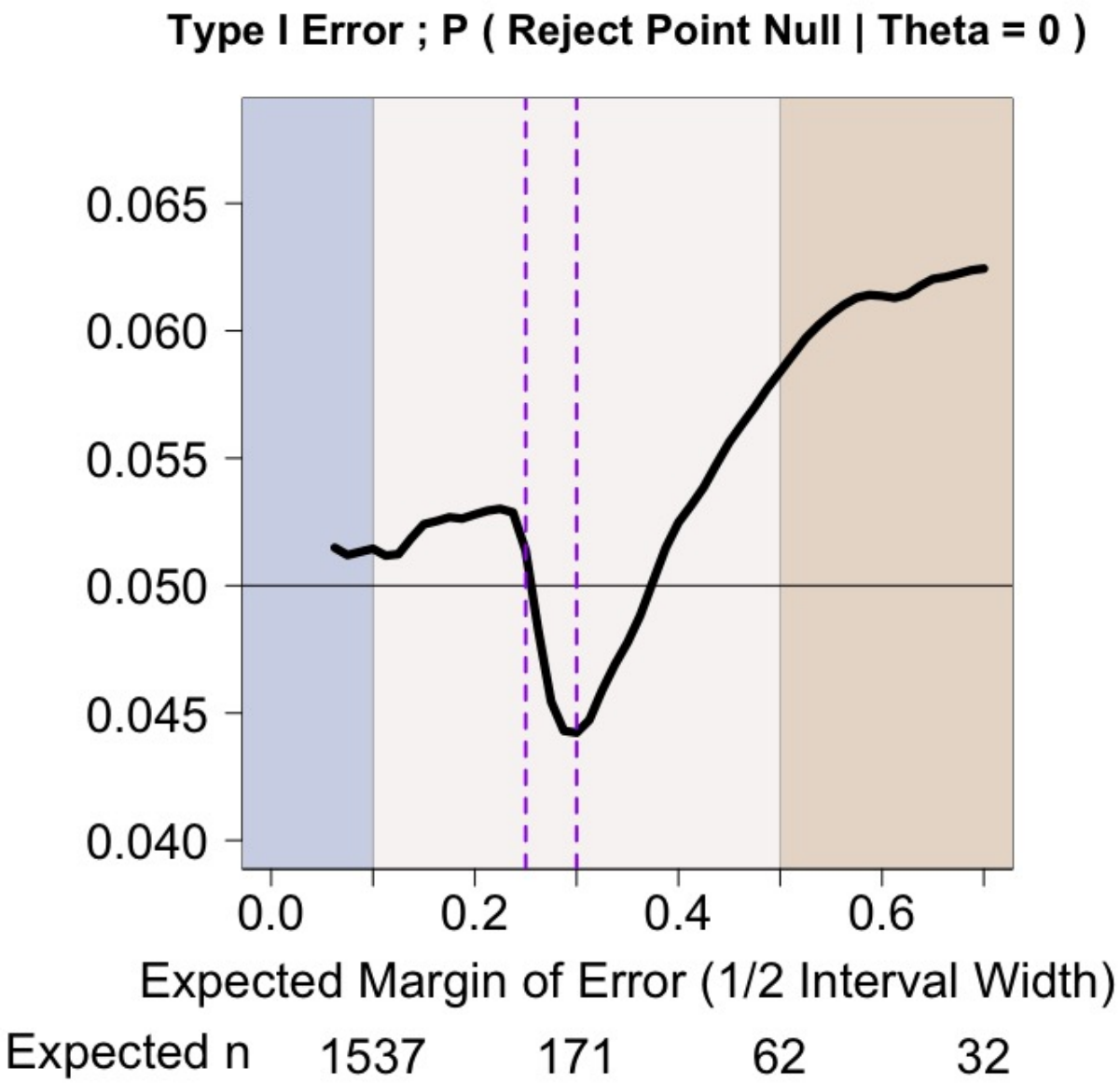
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Conclusions

1. AM SGPV novel design to follow studies until ruling out practially null or meaningful effects

2. With immediate stopping (k=0) and unlimited sample size, Type I error can be controlled through the wait time.

Thank you and questions