

Statistical Considerations for Assessing Rare Events in Single-Arm Studies

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Abstract
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In the absence of a control-arm, conservative assumptions are required. Using endpoints with low, well-defined response rates allows for smaller trial cohorts even when the treatment response is modest.

INTRODUCTION

FDA guidance permits single-arm designs for rare diseases, but proving efficacy without concurrent controls remains complex.

Rare diseases are often progressive, with low probability of spontaneous improvement.

Case Example:

Netherton Syndrome Investigator Global Assessment (IGA) response rates, based on Spesolimab trial data².

METHODS

Sample size calculations were done with a one-sided Boschloo test³.

Data assumptions were based on historical Spesolimab trial results:

- **First Endpoint:** A 1-point improvement on the IGA. Placebo response rates between 10% and 40% were evaluated vs a treatment response of 50%–75%.
- **Second Endpoint:** An IGA score of 0 or 1. Evaluated a fixed placebo response rate of 5% vs a treatment response rate of 25%–35%.

These randomized calculations were compared to a single-arm design. In single-arm scenarios, treatment efficacy was compared to a fixed threshold rather than a concurrent control group.

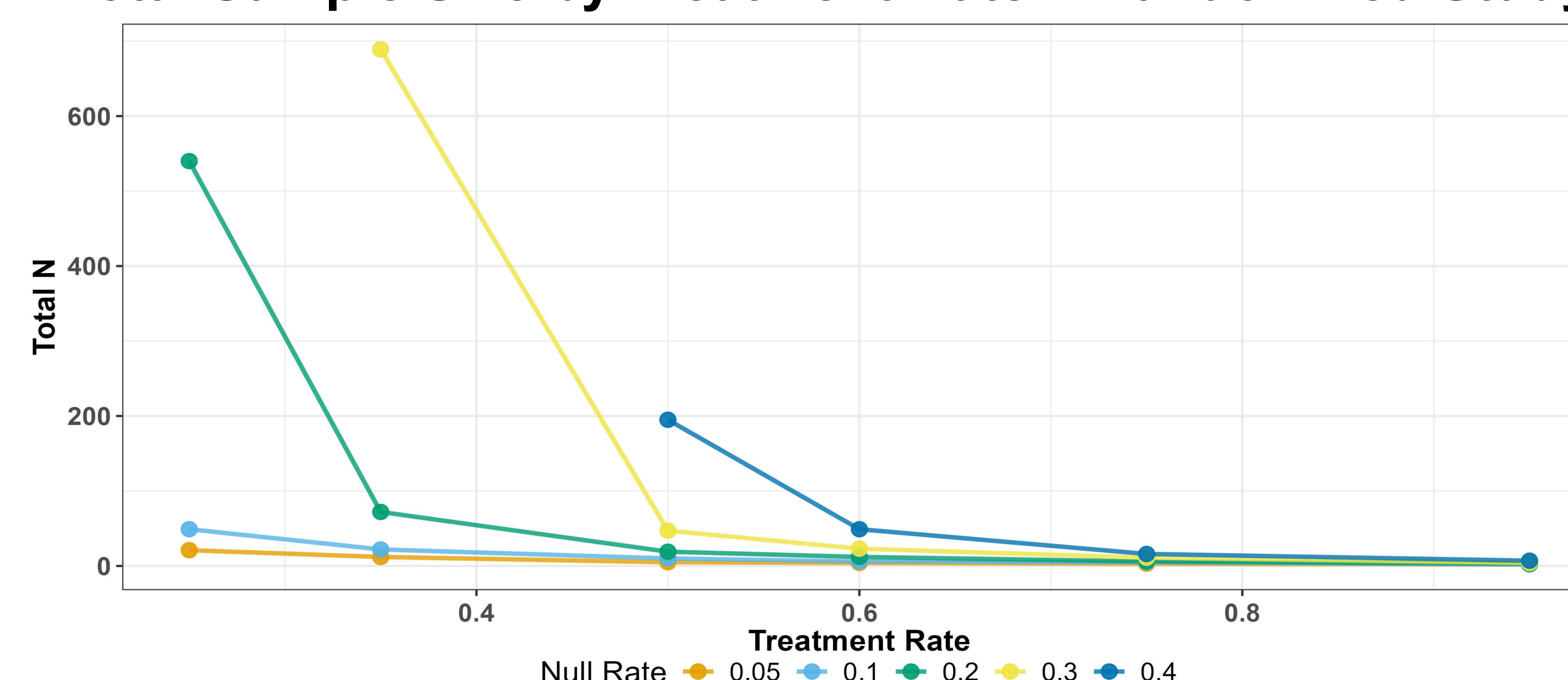
Across both scenarios, all evaluations used a **targeted power of 80%** and a **one-sided alpha of 0.025**.

RESULTS

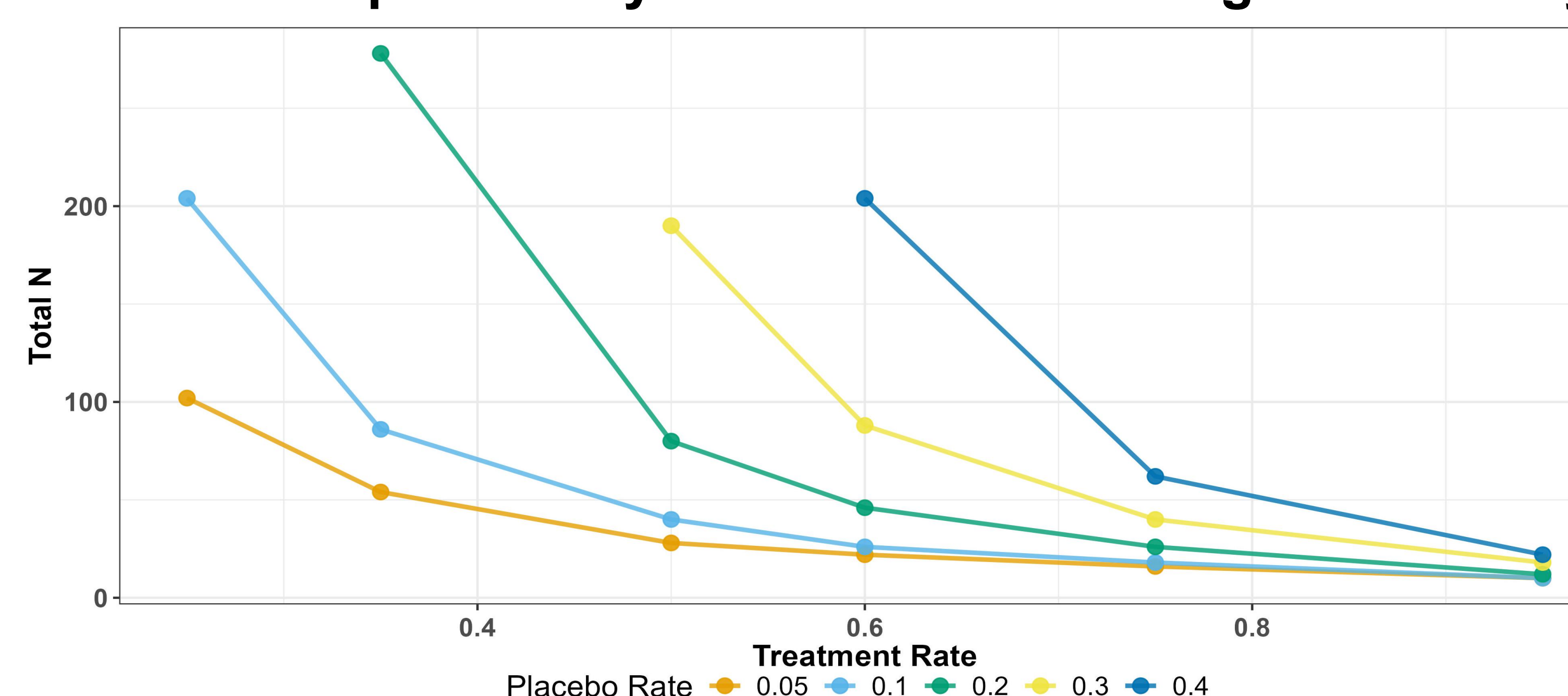
Required sample size depends heavily on endpoint choice and placebo assumptions:

- **1-Point Improvement Endpoint:** Highly sensitive to placebo rates.
 - **2-Arm Study:** 18–40 patients (10% placebo) vs. 62–784 patients (40% placebo)
 - **Single-Arm Study:** 16–195 patients
- **IGA Score of 0 or 1:** Low variability and highly efficient.
 - **2-Arm Study:** 54–102 patients
 - **Single-Arm Study:** 12–21 patients

Total Sample Size by Treatment Rate – Randomized Study



Total Sample Size by Treatment Rate – Single Arm Study



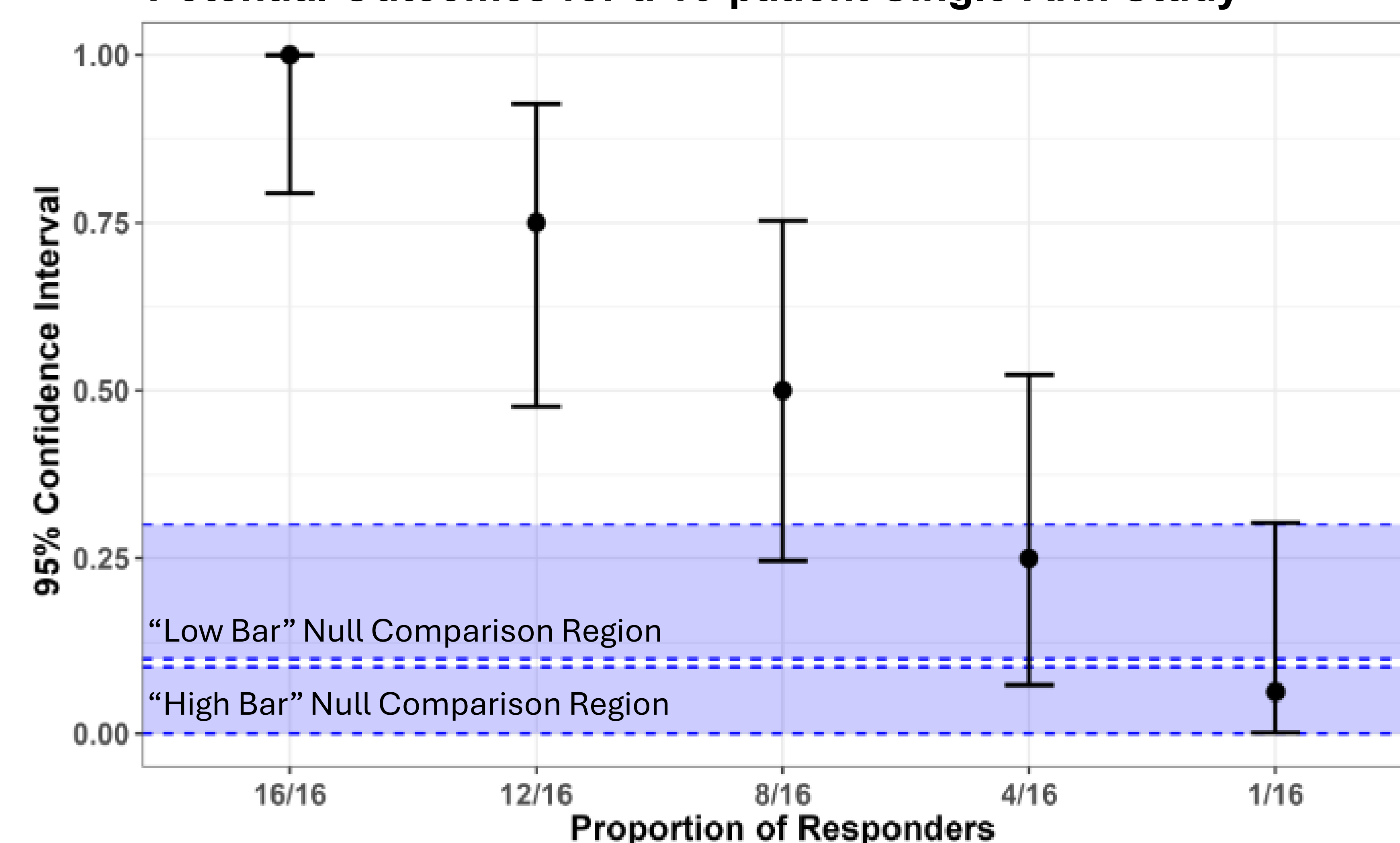
CONCLUSION

Without a control arm, regulators mandate conservative baseline assumptions:

Unpredictable Placebo Responses: High variability forces strict assumptions, significantly inflating required sample sizes to maintain power.

Well-Defined Response Rates: Low, predictable baseline rates permit much smaller trial cohorts—even with modest treatment effects.

Potential Outcomes for a 16-patient Single-Arm Study



Confidence intervals for different observed event rates in a proposed single-arm study with 16 patients compared to a null comparison region that represents a “low bar” for improvement compared to a “high bar” for improvement.

REFERENCES

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